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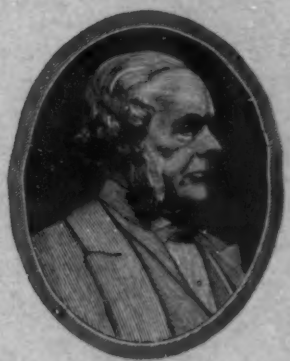

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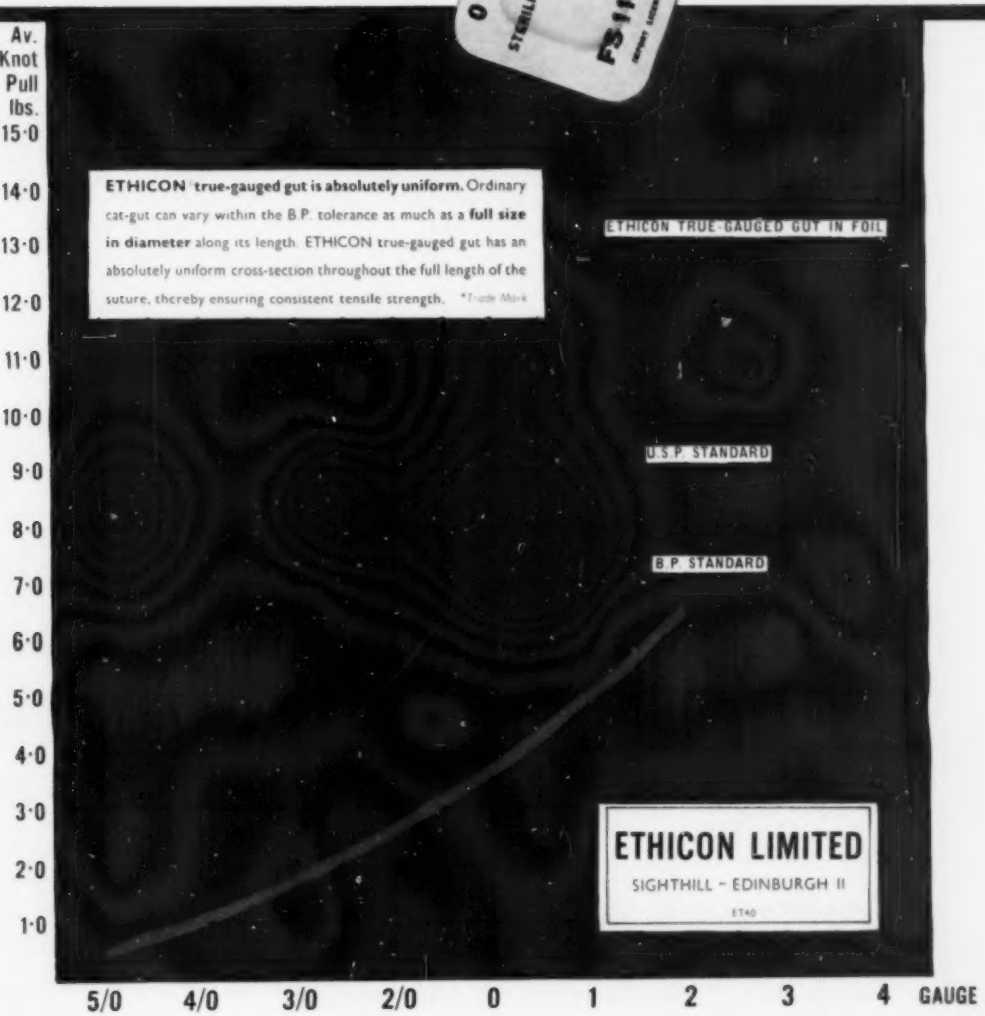

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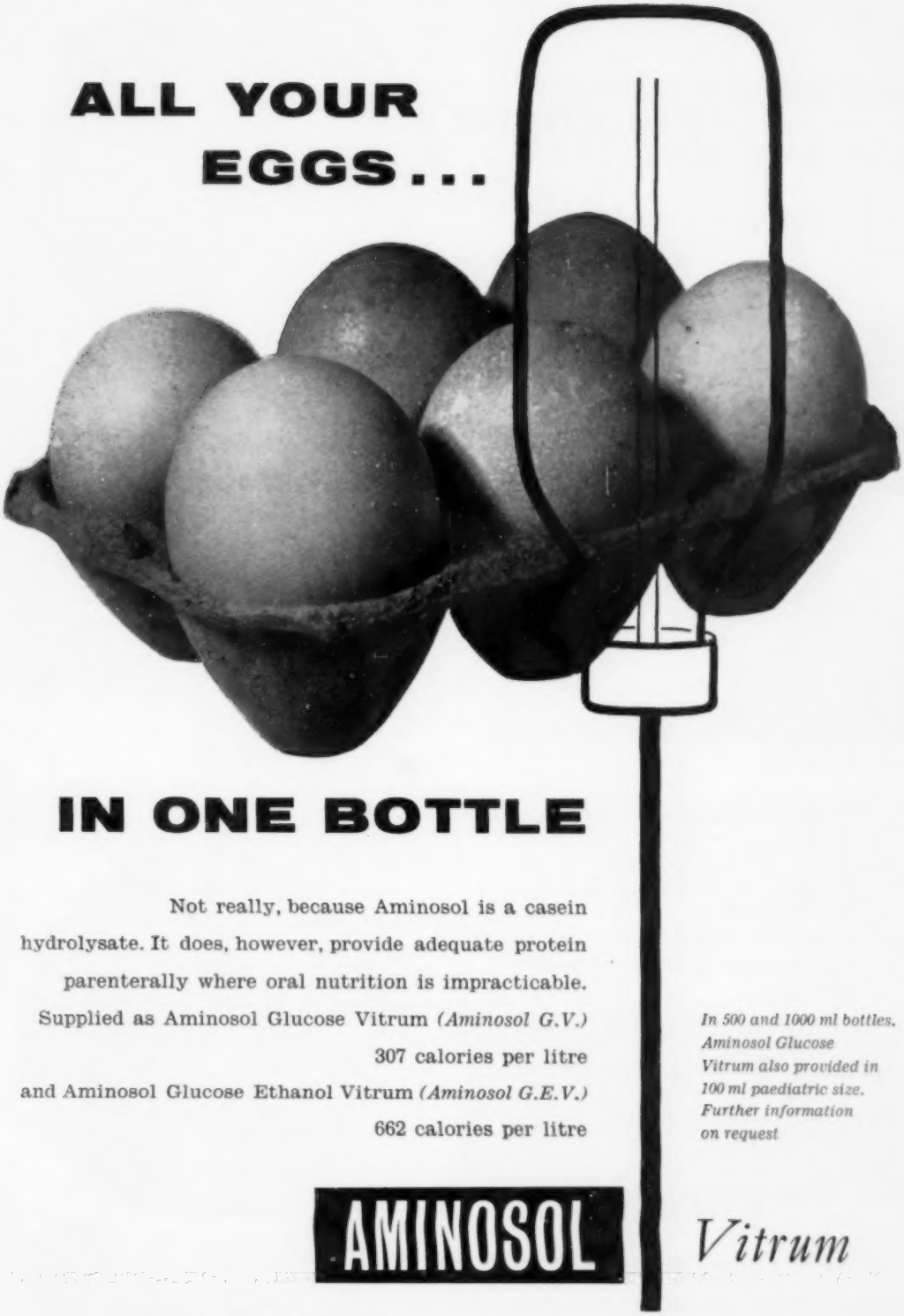

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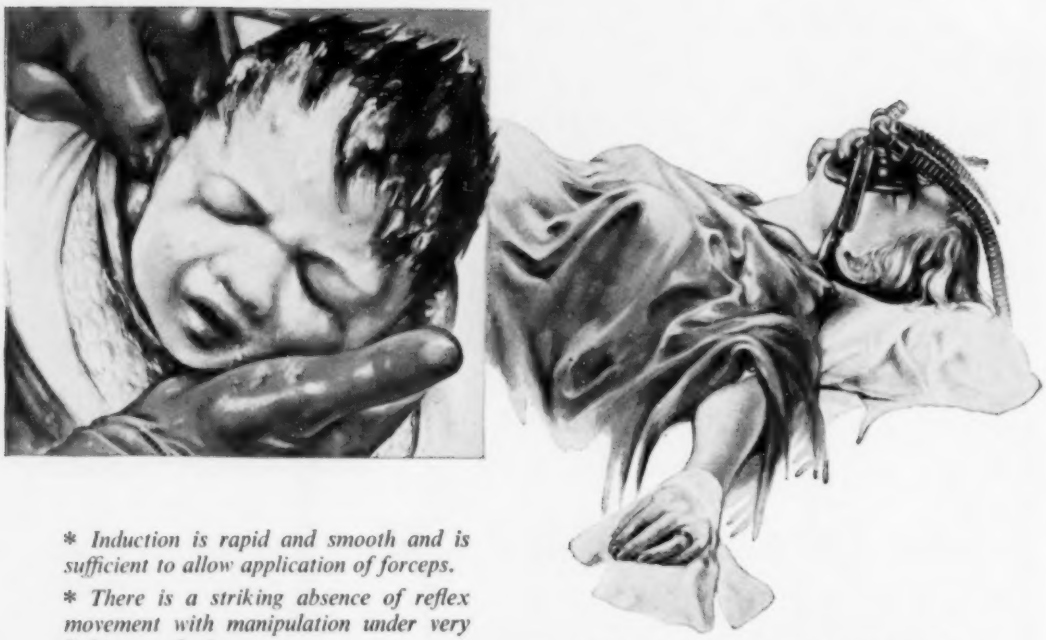

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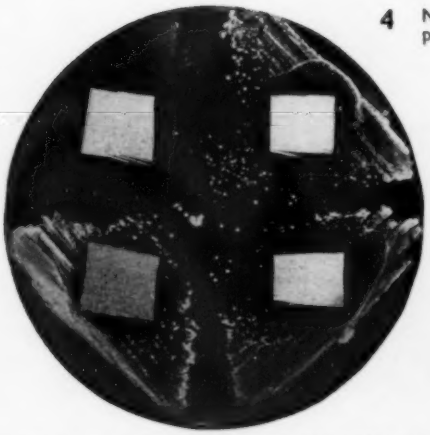

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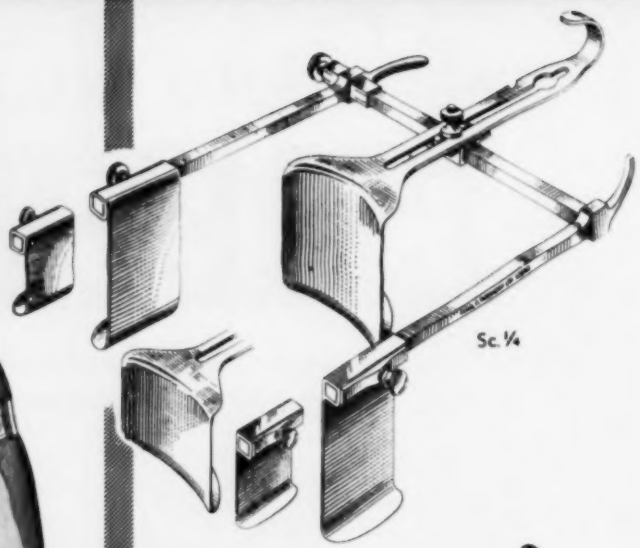

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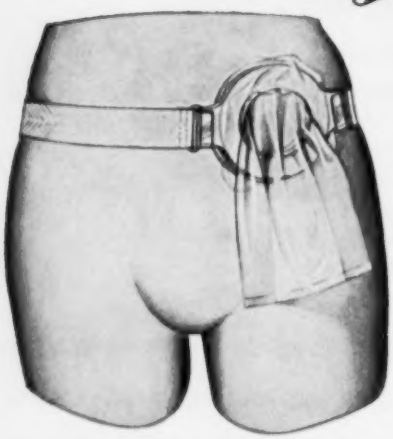

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THE DIAGNOSIS OF CARCINOMA OF THE LARGE BOWEL BY EXFOLIATIVE CYTOLOGY

BY D. J. OAKLAND

FROM THE QUEEN ELIZABETH HOSPITAL, EDGBASTON, BIRMINGHAM

SINCE the terminal 10 in. or less of the large bowel is the only part of that organ which can be inspected, the diagnosis of malignant disease may often depend on the symptoms and the results of radiological examination. The majority of malignant lesions in the large bowel occur in the sigmoid and recto-sigmoid (Fraser, 1938; Allcock, 1958), an area which may be difficult to demonstrate adequately by radiological techniques since one barium-filled loop may obscure the outlines of another (Ramsay, 1957). Further, lesions which should be within the theoretical reach of the sigmoidoscope may in fact be difficult or impossible to see owing to anatomical peculiarities or distortion by a pathological process. Where a lesion is demonstrated by radiology the clinician may still be left with a difficult differential diagnosis between an inflammatory and neoplastic process and be faced with a difficult decision between laparotomy and a policy of continued observation.

The success of exfoliative cytology in the diagnosis of malignant disease in other fields, notably gynæcology, suggests a useful place for this technique, if it could be applied, in the diagnosis of carcinoma of the large bowel. The few reports available (Wisseman, Lemon, and Lawrence, 1949; Blank and Steinburg, 1951; Bader and Papanicolaou, 1952; Rubin, Massey, Kirsner, Palmer, and Stonecypher, 1953; Galambos and Klayman, 1955; Raskin, Kirsner, and Palmer, 1958) on the application of cytology to the large bowel have been encouraging (*Table I*), but it is more difficult to obtain suitable specimens from this organ owing to its fæcal content.

The purpose of this paper is to report the results obtained from cytological examination in four series of patients with symptoms referable to the colon,

Table I.—RESULTS OF COLONIC EXFOLIATIVE CYTOLOGY REPORTED BY VARIOUS AUTHORS USING DIFFERENT TECHNIQUES (1949–58)

AUTHOR	TECHNIQUES	NO. OF CASES	CLINICALLY BENIGN	CYTOLOGICALLY NEGATIVE	CYTOLOGICALLY FALSE POSITIVE	CYTOLOGICALLY FALSE SUSPECTED POSITIVE	ACCURACY OF NEGATIVE CASES	CLINICALLY MALIGNANT	CYTOLOGICALLY POSITIVE	CYTOLOGICALLY SUSPECTED POSITIVE	CYTOLOGICALLY FALSE NEGATIVE	ACCURACY OF POSITIVE CASES
Wisseman and others, 1949	Smears during sigmoidoscopy	110	82	75	1	—	Per cent 91·5	28	9	7	12	Per cent 57
Blank and Steinburg, 1951	Smear of lesion during sigmoidoscopy	66	21	21	—	—	100	45	29	—	16	64
	Smear below lesion	21	2	2	—	—	100	19	1	—	18	5·4
Bader and Papanicolaou, 1952	Rectal washing through sigmoidoscope. Colonic lavage	200	161	159	2	—	98	19	14	4	1	73·7
Rubin and others, 1953	Colonic lavage	55	22	22	—	—	100	33	27	—	6	81
Galambos and Klayman, 1955	Colonic lavage: Method 1 Method 2	58	32	32	—	—	100	9 17	2 14	— —	7 3	22 82
Raskin and others, 1958	Colonic lavage: 1 Series 2 Series	135 82	131 61	4 1	— —	— —	97 98	48 21	37 20	— —	11 1	77 95

the last series consisting of patients referred for cytology since the technique has been offered as an experimental clinical service in the hospital.

THE METHOD OF COLLECTING CYTOLOGICAL SPECIMENS FROM THE COLON

Preparation of the Bowel.—Adequate cleansing of the colon is essential. The following technique of preparation is now used routinely and gives satisfactory results: Each patient is given enemas of normal saline night and morning on the two days preceding the collection of specimens. During both the days the patient takes one tablet of a contact laxative (Dulcolax) three times a day, and for the 24 hours preceding the collection of specimens he has a fluid diet only. On the morning of the day of the examination the patient receives a further saline enema as early as possible.

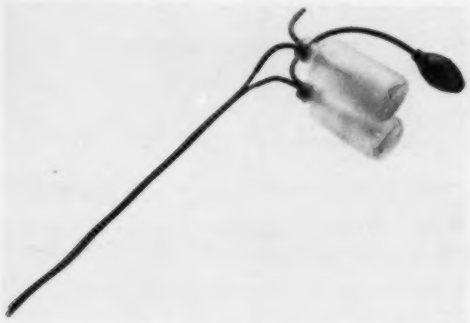

FIG. 396.—Modified rectal washing apparatus (250-ml. reservoir).

Collection Techniques.—Specimens are collected either by a colonic lavage technique or by rectal washing during sigmoidoscopy. Rectal washing is performed, using a modification of the apparatus (*Fig.* 396) originally described by Loeb and Scapier (1951) (Oakland, 1957, 1959), in cases where the clinician requests an opinion on the cytological content of the large bowel during sigmoidoscopy, or in cases where a lesion of uncertain nature is within the range of the instrument. The colonic lavage technique is now the standard method of collecting specimens and is used in all cases.

Colonic Lavage Technique (*Fig.* 397).—The patient lies in the left lateral position on an operating table or other suitable examination couch where the head-down and head-up position can easily be obtained. The sigmoidoscope is introduced as far as possible without causing any discomfort to the patient, and then a wide-bore rectal tube is passed into the bowel through the instrument, which is then withdrawn. 400 ml. of normal saline, at room temperature, is then run into the bowel through a funnel and rubber tubing. If the site of the suspected lesion is in the sigmoid colon the saline is washed in and out of the bowel for several minutes. During

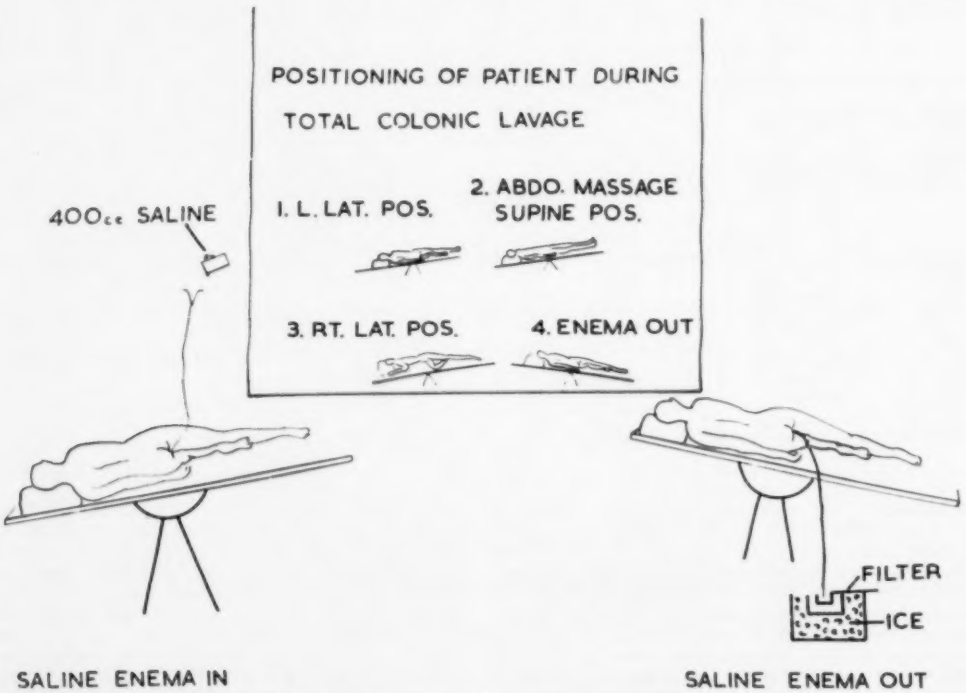

FIG. 397.—Technique of saline lavage for the collection of exfoliated cells from the large bowel.

this washing process the lower abdomen is gently massaged to encourage the flow of the saline within the sigmoid and ascending colon. In cases where the site of the colonic lesion is unknown and no assistance has been gained from radiological examination, a more elaborate technique of total colonic lavage is used. After the saline has been introduced the rectal tube is spigoted off and the patient lies on his back in the head-down position. The abdomen is massaged for 2 min. and the patient then turns on to his right side. Further gentle massage is carried out until the saline can be balloted within the cæcum. The patient then returns to the left lateral position and the head of the table is raised. The saline is collected through the rectal tube over the next 5 min., the emptying of the large bowel being encouraged by gentle abdominal massage.

The saline lavage specimen is filtered through two ordinary tea-strainers, placed one inside the other, directly into a beaker which is surrounded by iced water. The tea-strainers trap any solid fæcal debris or strands of mucus. The specimen is immediately centrifuged at 4500 r.p.m. for 3 min. The supernatant fluid is poured away and the deposit is spread on to frosted glass slides, normally two slides being required for the deposit from each centrifuge tube. The smears are immediately fixed in a 50 per cent alcohol-ether mixture.

The aim of the technique is to obtain fixed smears in the shortest possible time after the collection of the specimen from the patient, so as to reduce to the minimum cell degeneration, with its consequent distortion and difficulty in interpretation. In nearly all cases two separate specimens are collected from each patient, 400 ml. of solution being used on each occasion. About 50 per cent of the solution is returned in the first examination, but 75 per cent or more is evacuated on the second examination.

Processing in the Laboratory.—Smears are fixed for a minimum of 1 hr. and then stained, using the Papanicolaou technique (Papanicolaou, 1942). Each smear is scanned by a cytology technician and areas of cell interest are marked, using a diamond object marker. Smears are subsequently re-examined by the cytologist with particular reference to the marked areas.

Time required for Collection and Processing.—Two separate saline enema specimens can be collected from a patient in 30 min., the first specimen being centrifuged and smears prepared whilst the second specimen is being collected. The smears are stained after 1 hour's fixation, the staining technique taking about 1 hr. Each smear can be scanned by a competent cytology technician in 10 min., although rather longer may be required if the smear is very cellular. This means that if specimens are collected at the beginning of the day, processing and scanning can usually be completed the same day, though in point of fact the scanning is often deferred until the following day to allow the Canada balsam cement to set hard, since the diamond object marker is likely to move the cover-slip when fresh smears are scanned.

THE DIAGNOSIS OF CARCINOMA OF THE LARGE BOWEL BY EXFOLIATIVE CYTOLOGY

The characteristics of cells exfoliated from the normal and abnormal large bowel were ascertained initially by examination of specimens collected from groups of patients with normal lower alimentary tracts, malignant disease of the rectum, and non-specific inflammatory disease, e.g., ulcerative colitis (Oakland, 1957, 1959). Following this initial work, three series of patients were examined, the Trial Diagnostic Series, with a view to establishing the diagnostic accuracy of the technique and discovering the technical difficulties in collecting and processing the material.

Reporting of Smears.—In the first three trial diagnostic series smears were reported as 'negative', 'suspicious', 'positive', or 'unsatisfactory' material. At present smears are reported as 'negative', 'positive', or 'inconclusive'. It is felt that this simpler technique of reporting smears is of more value to the clinician than the more elaborate technique used by Bader and Papanicolaou (1952).

Table II.—TRIAL DIAGNOSTIC SERIES

	Series 1	Series 2	Series 3
	Rectal Washing	Colonic Lavage	
Number of patients examined	54	85	36
Proven cases of cancer	22	25	18
Cytology positive	16	15	15
	Accuracy 73 per cent	Accuracy 60 per cent	Accuracy 83 per cent
Cytology suspicious	1	—	—
Cytology negative (false)	4	3	2
Unsatisfactory specimens	1	7	1
Proven cases without cancer	30	59	15
Cytology negative	25	45	14
Cytology positive (false)	3	5	—
Unsatisfactory specimens	2	9	1
Diagnosis not proven	2	1	3

The Trial Diagnostic Series of Cases.—The absolute diagnosis in these series of cases was established by laparotomy, by biopsy, or by follow-up for a minimum period of 9 months. The results obtained in the three trial diagnostic series are set out in *Table II*, the first series of patients being examined by the rectal washing technique and the other two by the colonic lavage technique. In all the series if unsatisfactory material was collected from patients

who were subsequently proved to have a cancer, they were counted as 'false negative'. This has considerably reduced the accuracy in the second trial diagnostic series where the colonic lavage technique was used. In the third trial diagnostic series unsatisfactory material was obtained from only one case of proven carcinoma. This improvement reflects the much greater care which was taken with the preparation of the patient in this third series, and is in accord with the reports of others (Galambos and Klayman, 1955; Raskin and others, 1958).

In the first trial diagnostic series in which the rectal washing technique was used to collect specimens, only 1 patient with cancer yielded unsatisfactory material since only a limited length of colon was being washed and any solid fæcal material could be deliberately avoided.

It will be noted that in the three series the number of false positive reports decreases and in the third series the accuracy in those patients who were proved not to have a cancer was 100 per cent. This improvement reflected the increasing experience of the observer. Such causes of false positive reporting as overstaining and atypical cells exfoliated from inflammatory surfaces were recognized with greater ease as the number of patients increased. It is obviously important that the incidence of false positive cases should be reduced to zero, since a false positive diagnosis may wrongly influence the clinician to advise operation.

The site of the malignant lesions in each of the three series is shown in *Table III*. The number of neoplasms occurring in the distal end of the colon in this series reflects the common experience of the site of malignant disease of the large bowel. Unfortunately, the number of lesions occurring in the proximal colon was insufficient to give results which are significant. The diagnostic accuracy in the three series obtained in lesions of the sigmoid and recto-sigmoid can be regarded as most satisfactory. Since it is in these areas where help is often required in resolving the nature of lesions seen on radiological studies, the results obtained in the trial diagnostic series seem to suggest that the exfoliative cytology technique can be of value to the clinician.

It is difficult to compare the results obtained by cytology with those obtained by radiology. Radiological reports may not state categorically, but only infer, the presence of a carcinoma from the appearance of the barium-filled bowel. However, a similar type of report is not possible in cytological analysis since the presence of malignant cells in the smear is positive evidence of the presence of a carcinoma. Nevertheless there seems little doubt that a combination of the two techniques is bound to give an increased diagnostic accuracy and this in fact was the finding in the trial diagnostic series of cases.

Apart from the number of cases where unsatisfactory specimens were obtained, there did not appear to be any significant difference between the results obtained by using either the rectal washing or saline enema technique. However, the saline enema technique is now used routinely since it is felt that better cell specimens are likely to be obtained if the collecting medium actually irrigates the lesion. The rectal washing technique collects cells by the same method when the lesion is in the distal colon, but in lesions in the more proximal reaches of the bowel the irrigating material can only collect cells which have already exfoliated and have passed down the lumen of the bowel.

The Clinical Diagnostic Series.—The experience obtained in the three trial diagnostic series suggested that exfoliative cytology might be offered as an experimental clinical service in the hospital. This latest series (*Table IV*) illustrates in what type of case the exfoliative cytology technique has proved to be most valuable.

In this series 31 cases were examined, 27 by the colonic lavage technique and 5 by the rectal washing technique—in 1 case both techniques were used.

Table III.—Trial Diagnostic Series

Site of Carcinoma	Cytological Results							Unsatisfactory Material		
	Positive			*Suspicious*	*Negative*					
	Series 1	Series 2	Series 3	Series 1	Series 1	Series 2	Series 3	Series 1	Series 2	Series 3
Rectum	1	1	2	—	—	—	1	—	—	—
R. sigmoid	5	4	2	—	1	—	—	—	—	—
Sigmoid	8	6	7	1	1	2	—	1	1	—
L. colon	—	—	1	—	1	—	—	—	1	—
T. colon	1	2	—	—	—	1	1	—	3	—
R. colon	—	—	1	—	1	—	—	—	—	—
Cæcum	1	2	—	—	—	—	—	—	2	1

Table IV.—Trial Clinical Series

Total number of patients examined	31 cases
Patients with cancer	9
Cytology positive	7 (Accuracy 78 per cent)
Cytology negative (false)	2
Patients without cancer	21
Cytology negative	21 (Accuracy 100 per cent)
Cytology positive (false)	0
Diagnosis not proven	1

Nine patients were subsequently proved by operation to have a carcinoma, and 7 of these had positive cytological smears, an accuracy of 78 per cent, the 2 false negative cases being patients who had carcinoma of the cæcum. Twenty-one patients had non-malignant conditions of the large bowel and none of these gave positive smears, an accuracy of 100 per cent. In 1 patient the smears were reported as inconclusive on two occasions and the absolute diagnosis still remains in doubt, although it seems likely that the patient has a non-malignant condition.

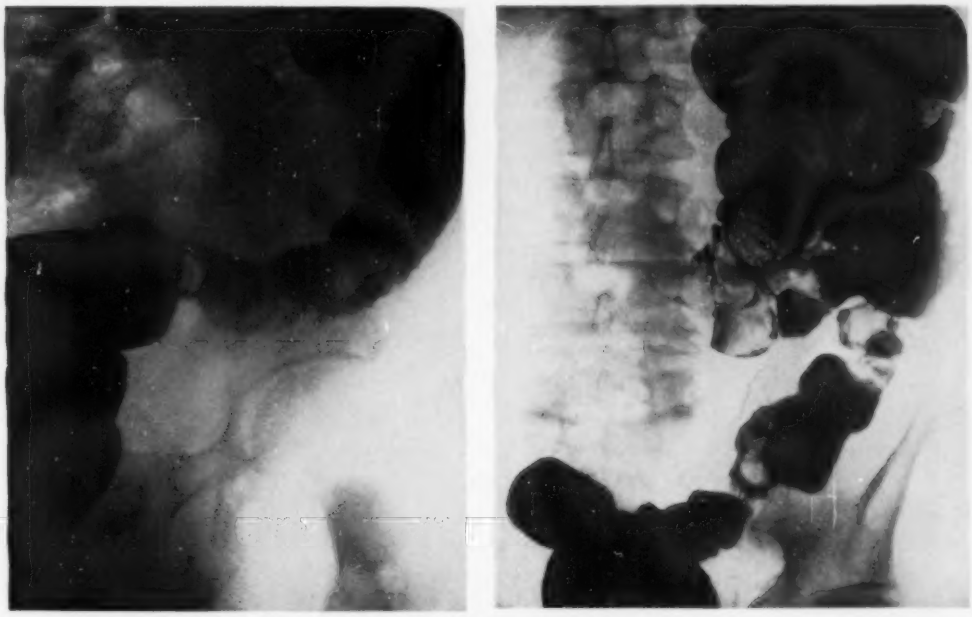

FIG. 398.—Barium enema from *Case* 1.

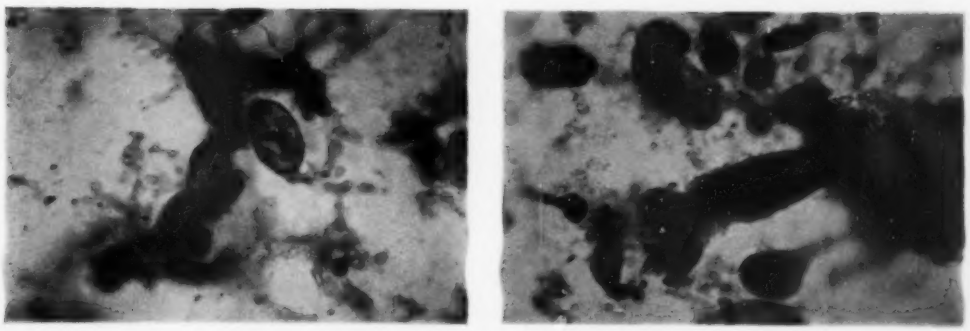

FIG. 399.—Exfoliated malignant cells from *Case* 1.

CASE REPORTS

The following cases illustrate the value of exfoliative cytology in the differential diagnosis of lesions of the large bowel. *Cases* 1–5 are taken from the Clinical Diagnostic Series and *Cases* 6–8 from the Trial Diagnostic Series.

Case 1.—T. B., a 76-year-old male patient with a history of increasing constipation and occasional melæna over the previous two years. On examination he was hypertensive but abdominal and rectal examination was negative. A barium enema showed that the rectum was empty but the remainder of the colon contained considerable fæcal material (*Fig.* 398). The radiologist was of the opinion that there was no organic obstruction, but the sigmoidoscope could not be passed further than 7 cm. and a little blood-tinged mucus was seen at this site. However, a biopsy at this site was reported as showing

FIG. 400.—High-power photomicrograph of histological section from *Case* 1. (× 150.)

normal rectal mucosa infiltrated with chronic inflammatory cells, with no evidence of malignancy. In view of the equivocal findings, specimens were collected for cytological examination by the saline enema technique and malignant cells were seen in the smears (*Fig.* 399).

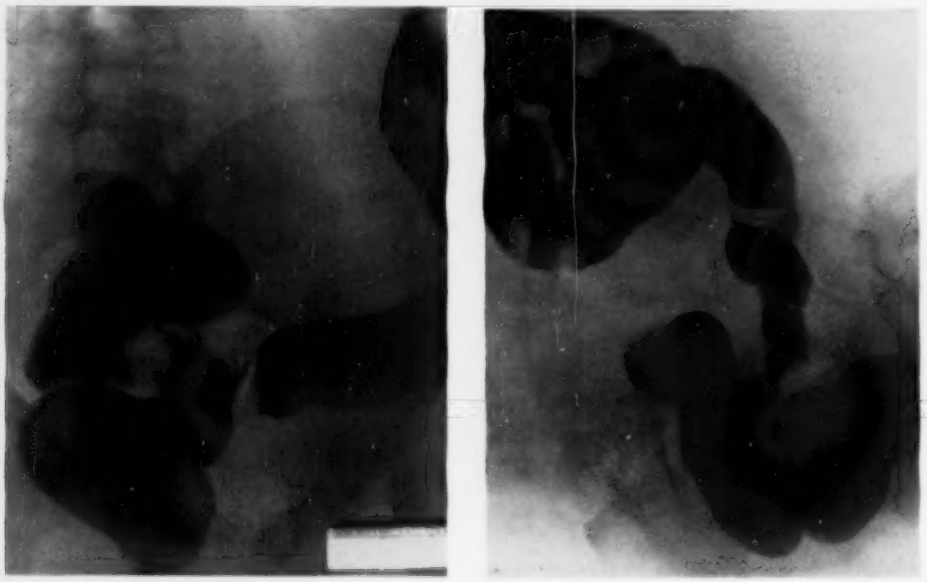

FIG. 401.—Barium enema from *Case* 2.

FIG. 402.—Exfoliated malignant cells from *Case* 2.

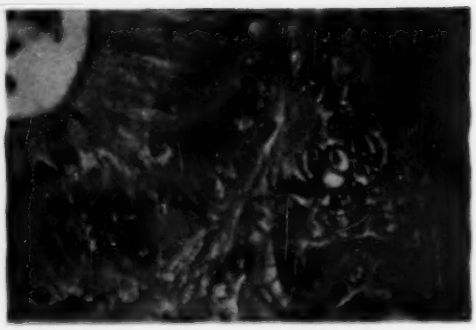

FIG. 403.—High-power photomicrograph of histological section from *Case* 2. (× 150.)

Laparotomy confirmed the presence of a small annular carcinoma of the sigmoid (*Fig.* 400), a partial colectomy being performed.

Case 2.—E. T., a 60-year-old obese female patient, was investigated for vomiting and intermittent melæna accompanied by occasional attacks of diarrhœa. On examination, she was hypertensive and her obesity made abdominal examination difficult, but there was some suggestion of a mass in the left iliac fossa. Rectal examination was negative. A barium enema showed no definite abnormality except in the proximal part of the sigmoid colon, which contained a segment which would not adequately distend (*Fig.* 401). Sigmoidoscopy showed a rough granular area of mucosa 13 cm. from the anus, but a second sigmoidoscopic examination showed no abnormality up to 17 cm. In view of these equivocal findings specimens were collected for exfoliative cytology by the saline enema technique and groups of malignant cells were seen (*Fig.* 402). The patient was examined under anæsthetic and no physical signs could be found on abdominal or pelvic examination. Laparotomy was performed and an adenocarcinoma of the sigmoid colon was revealed (*Fig.* 403), and a left partial colectomy was performed.

Case 3 (Previously reported by Kunkler and Rains, 1959).—N. F., a 63-year-old female patient with a history of having passed blood per rectum on one occasion associated with some slime. She also gave a history of some alteration of bowel habit inasmuch as she was passing more frequent stools. On examination, she was in poor general health, being hypertensive, with auricular fibrillation and aortic stenosis. Abdominal examination revealed no physical signs, but on rectal palpation a firm mass could be felt in the pouch of Douglas. A barium enema showed no abnormality of the large bowel (*Fig.*

404), and sigmoidoscopy up to 6 in. appeared normal, although a little blood-stained mucus was seen in the lumen of the rectum. In view of the patient's poor medical condition and the equivocal findings on examination it was felt that laparotomy was unjustified, but specimens were collected for exfoliative cytology by the saline enema technique. Smears prepared from this material were found to contain malignant cells (*Fig.* 405). In view of these findings, a laparotomy was performed and a small carcinoma of the distal portion of the sigmoid colon was found. A left partial colectomy was performed and the tumour was found to be an ulcerating adenocarcinoma 4 cm. in diameter (*Fig.* 406).

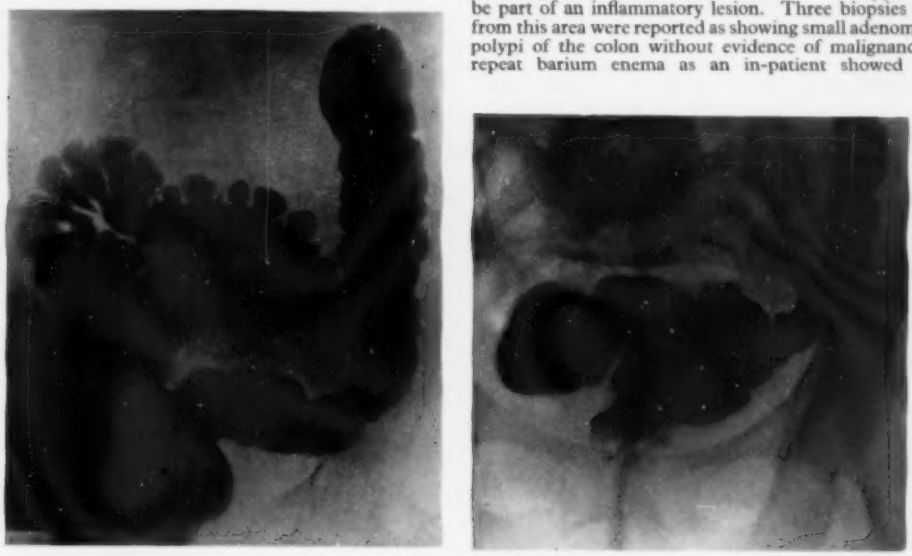

FIG. 404.—Barium enemas from *Case* 3.

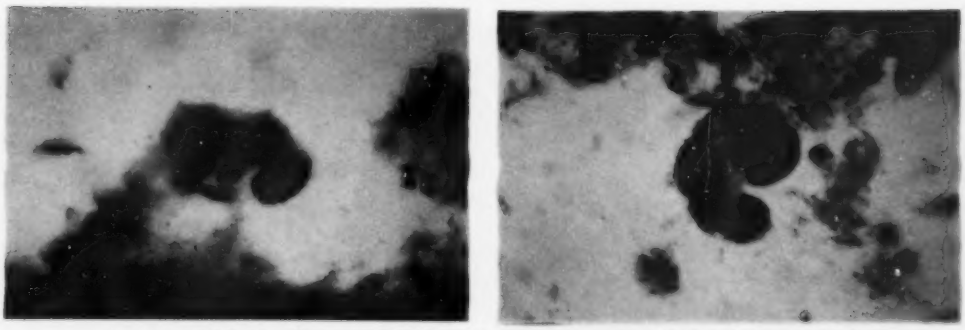

FIG. 405.—Exfoliated malignant cells from *Case* 3. (By kind permission of E. & S. Livingstone Ltd.)

Case 4.—W. D., a female patient of 77 years with a 3-months' history of left-sided abdominal pain and back pain. She also complained of melæna. Examination revealed no abnormality in the abdomen but on rectal palpation an indefinite mass could be felt about 4 in. from the anus. A barium enema showed diverticulosis of the sigmoid and a narrowed segment in the apex of the sigmoid loop (*Fig.* 407). Sigmoidoscopy in the out-patient clinic revealed a normal bowel up to 4 in., but there was some dark blood in the lumen. Repeat sigmoidoscopy in the hospital showed a small polypoid lesion in the sigmoid colon together with œdematous mucosa which appeared to be part of an inflammatory lesion. Three biopsies taken from this area were reported as showing small adenomatous polypi of the colon without evidence of malignancy. A repeat barium enema as an in-patient showed three

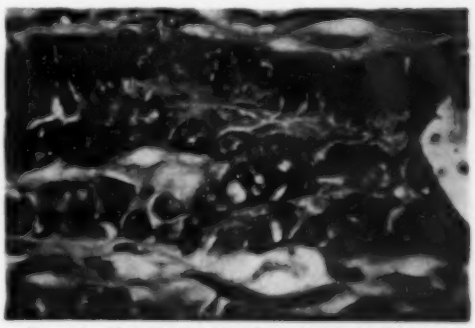

FIG. 406.—High-power colour photomicrograph of histological section from *Case* 3. (× 150.)

sigmoid diverticula containing barium residues from a previous enema, together with a narrow area without any hold-up in the flow of the barium which was thought to be due to diverticulitis. Specimens were collected for exfoliative cytology by the saline enema technique. All these contained numerous adenocarcinoma cells (*Fig.* 408). Laparotomy was performed and the patient was found to have a cicatrizing growth in the lower sigmoid (*Fig.* 409). A left partial colectomy was performed.

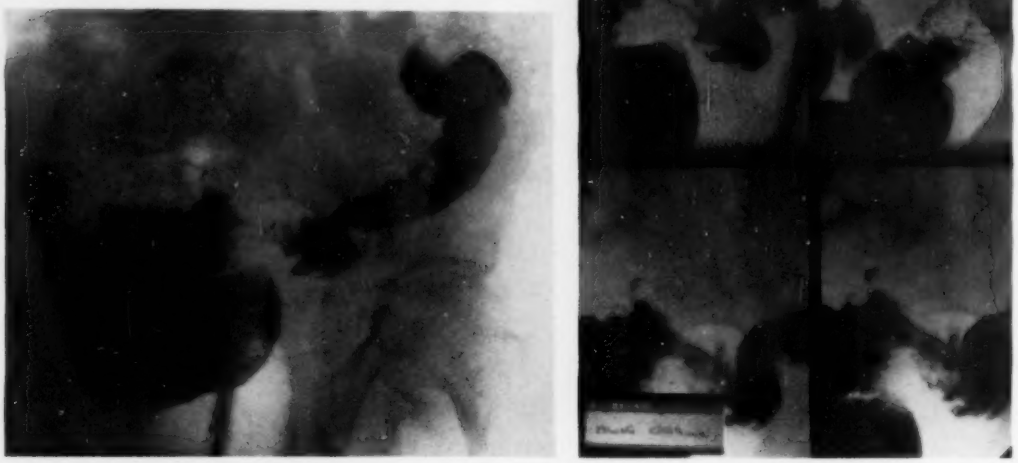

FIG. 407.—Barium enemas from *Case* 4.

FIG. 408.—Exfoliated malignant cells from *Case* 4.

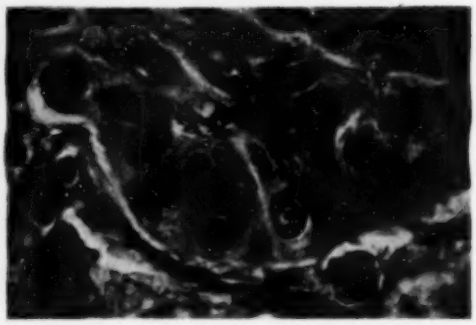

FIG. 409.—High-power photomicrograph of histological section from *Case* 4. (× 150.)

Case 5.—W. R., a 72-year-old male patient with a normal bowel habit, presented with a sudden rectal hæmorrhage. Abdominal examination was normal, but on rectal palpation a soft polypoid mass could be felt high up in the rectum. Barium enema showed no abnormality of the large bowel or hold-up in the flow of the enema. Sigmoidoscopy revealed two small polypi at 6 in. Both were removed for biopsy and were reported as being adenomatous polypi of the large-bowel type, showing focal atypicalities of the lining epithelial cells. Specimens were collected for exfoliative cytology and the smears contained a few groups of cells which were suspicious of malignancy and which were similar to the abnormal cells seen in the biopsy.

This patient was kept under observation and a further sigmoidoscopy some 5 months later revealed a polypus at 6 in. Biopsy on this occasion showed a well-differentiated adenocarcinoma and cytological specimens collected by the rectal washing technique contained numerous malignant cells. Laparotomy revealed the presence of an ulcerating adenocarcinoma of the rectosigmoid together with a further papilloma in the sigmoid colon. Abdomino-perineal excision of the sigmoid colon and rectum revealed further papillomata in the sigmoid colon.

Case 6.—J. C., a 62-year-old male patient who had previously had a papilloma of the distal sigmoid excised by diathermy. The pathologist reported that the papilloma showed "fairly well-differentiated glands arranged in a papillary fashion. There is no carcinoma at the base but the cytological appearances of the glands are atypical." The patient was kept under observation and 5 months later specimens were collected for cytological examination by the saline enema technique. These smears showed definite malignant cells and sigmoidoscopy revealed a new polypus in the distal sigmoid. Laparotomy was then performed and this polypus was excised locally. On this occasion the pathologist reported that the polypus consisted of a "papillary arrangement of de-differentiated rectal glands which are irregular. Some irregularity of structure

and invasion of the stroma. The appearances of this specimen are those of carcinoma."

Case 7.—E. P., a 60-year-old female patient who was seen on June 10, 1959, complaining of a long history of constipation terminating in an attack of diarrhœa lasting a week. On examination she showed an iron deficiency as she was anæmic, but there were no other physical signs. Her hæmoglobin was 74 per cent and a barium enema

FIG. 410.—Exfoliated columnar epithelial cells from the colon of *Case* 7 showing early degenerative changes.

showed a persistent spasm of the lower sigmoid colon, but no other abnormality. Sigmoidoscopy to 18 cm. revealed no lesion. Laparotomy was performed on July 2 and the sigmoid colon and left Fallopian tube were found to be involved by a hard fixed nodular mass lying at the left pelvic brim in front of the sacrum. The mass appeared to be neoplastic, but its origin was doubtful. A biopsy was taken which was reported as showing secondary infiltration with papillary columnar-celled adenocarcinoma which could have originated from the colon or ovary. Colonic lavage was performed and no malignant cells were seen, although numerous normal and degenerate normal colonic cells were present (*Fig.* 410). In view of the negative cytology it seemed reasonable to assume that the primary site of the neoplasm was from the ovary and therefore the patient was given a course of radiotherapy, with very satisfactory results. Fourteen months after completion of her treatment the mass had shrunk to a small indurated area which was palpable on examination.

Case 8.—E. A., a 61-year-old female patient investigated in March, 1958, for attacks of alternating diarrhœa and constipation of 1 month's duration associated with bleeding per rectum. Physical examination revealed no significant signs apart from slight abdominal distension. Laparotomy was performed on March 31 and she was found to have a large firm mass at the rectosigmoid junction involving the small bowel and bladder. An abscess cavity was present in the pelvis. A left inguinal colostomy was performed after the small bowel had been freed from the mass.

Following this operation she was kept under observation in the out-patient department, the differential diagnosis between diverticulitis and carcinoma not being established. Her general condition remained well, but she continued to pass small quantities of blood per rectum and, in view of this, specimens were collected for cytology by the saline enema technique on May 28 and were positive for malignant cells. The patient was re-examined on October 9, when, although her general condition remained satisfactory, clinical sigmoidoscopic examination revealed the edge of a large malignant ulcer and biopsy at this time confirmed that it was a well-differentiated adenocarcinoma.

DISCUSSION OF CASES

All the cases in the trial clinical series were examined by exfoliative cytology, since the diagnosis was in doubt even after the classical methods of investigation had been completed. The first 4 cases reported above illustrate the value of the technique to the clinician and in all it is fair to say that the decision to undertake a laparotomy was influenced by the cytological report. *Case* 1 is interesting, for, though the lesion was within the reach of the sigmoidoscope, examination of the specimen after operation showed that the biopsy had been taken at a point 2 in. distal to the site of the lesion. *Case* 2 illustrates how in the obese patient physical, sigmoidoscopic, and radiological examination may be difficult, but this feature does not hamper the collection of cytological material. In *Case* 3 the equivocal results of radiology and sigmoidoscopy in the presence of cardiac disease made the decision to perform exploratory laparotomy difficult, and in this case cytology clearly indicated the necessity for surgery.

Malignant change may occur in a papilloma of the colon and anything less than total biopsy may not give a true picture of the histological nature of the lesion. In those cases where there are more than one polyp a single biopsy may also be misleading. However, examination of these cases by exfoliative cytology does enable cells which have exfoliated from all the lesions to be inspected, particularly as the areas which have undergone malignant change exfoliate more readily (Coman, 1944). In *Case* 5 it was assumed that the rectal hæmorrhage was due to the benign adenomatous polypus, the presence of a carcinoma only being suggested by the cytology being reported as 'suspicious'. Later observation confirmed the early cytological report when biopsy showed the presence of a well-differentiated adenocarcinoma. *Case* 6 also illustrates how cytology gave warning in advance of biopsy of the malignant nature of a polypus. In *Case* 8 cytology proved useful in determining the nature of the obstructive lesion in a patient who had had a colostomy established for acute-upon-chronic intestinal obstruction. Finally, *Case* 7 illustrates that negative cytology of the distal colon may be useful.

CONCLUSIONS

The results of examining several series of patients show that it is possible to find malignant cells which have exfoliated from lesions at any site in the colon, although the technique appears to have its greatest value in resolving the nature of lesions in the sigmoid and rectosigmoid.

The method of collecting specimens is relatively simple but requires meticulous preparation of the patient, and the colon should be free of all solid fæcal debris. For this reason the collection of specimens from lesions in the proximal colon presents greater technical difficulties, since there is more likelihood of collecting fæcal debris which has escaped the preparatory enemas.

The minimum time should elapse between the collection of material and the fixation of the smears, since degenerate cells are difficult to interpret and cannot be used for diagnostic purposes.

The value of this new clinical test for carcinoma of the large bowel is demonstrated in the last series of patients, where the diagnosis of carcinoma of the sigmoid was not made by radiology or sigmoidoscopy.

There appears to be a short length of colon between the lower reliable limit of the barium enema and the upper limit of the sigmoidoscope where it is difficult to demonstrate the presence of a lesion; here cytology is particularly helpful in diagnosis.

The nature of papilloma of the colon and rectum can be more accurately determined by the collection of cells which have exfoliated from the entire surface of the lesion, than by chance biopsy which may miss the papilloma which has undergone malignant degeneration.

SUMMARY

1. The value of diagnosis of carcinoma of the large bowel by cytology in the region of the sigmoid and rectosigmoid is suggested.

2. The method of preparation of the colon for cytology is described.

3. The two methods which were used to collect specimens for cytology in four series of patients are described.

4. Following the use of these two techniques in three series of patients the diagnostic technique was offered as an experimental clinical service and the results of the last series are presented with case-histories to illustrate the type of problem where cytology is most helpful to the clinician.

5. Exfoliative cytology appears to be a useful diagnostic technique for carcinoma of the colon particularly in those lesions which lie in the sigmoid and rectosigmoid. It is also of value in determining the nature of papilloma of the colon and rectum.

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POST-OPERATIVE SEPSIS

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THIS paper discusses the role of pre-operative skin antiseptics with emphasis on iodine in post-operative sepsis, the effect of blanket sterilization on the sepsis rate, together with some observations on surgeons' gloves and air contamination of wards and theatres, in a study of 1811 operations in a provincial group hospital.

INTRODUCTION

This study arose through the author being one of a working party of the Public Health Laboratory Service undertaking a survey of post-operative sepsis in various hospitals in the country, the results of which are published elsewhere (*Lancet*, 1960), and the method used for registering patients and recording their progress was that devised by the working party. During the survey opportunity arose of considering the role of other factors not included in the original survey, and it is with one of these—the possible relation of the skin antiseptic applied just before operation—that the first part of this paper is concerned. The other factors—contamination of surgeons' gloves, of blankets, and of the air in theatres and wards and their possible relation to sepsis—will be dealt with later.

METHODS

The cases were male and female surgical patients admitted either as emergencies or from the waiting list to the general surgical wards of two hospitals, A,

of about 270 beds, and B of 200 beds, in a provincial town in England, which are combined and administered as a group hospital. The hospitals serve an urban and rural population of 150,000 and the cases were of the type to be expected in such a population. Four surgeons were concerned, three general and one with a preference for orthopædic work. With the exception of three types of case—genito-urinary, operations involving the rectum, and open fractures—no attempt was made to select the cases, and the method therefore, with these exceptions, was to accept all admissions during a certain period, Nov. 1, 1957, to June 30, 1959, in the study. The reason for not including the exceptions was that it was considered that they might show a tendency to become septic from the nature of the site or lesion. The wards were 6 in number, one male and one female in each hospital and a male and female convalescent ward in Hospital B. In Hospital A the average was 22 beds to the ward, in Hospital B, 25.

The method of recording cases was as follows. Male and female patients admitted to the surgical wards were examined and a record made on a special form of their names, ward, hospital number, age, sex, and date of admission. This form was the one devised by the Public Health Laboratory Service working party for use in the survey. A nasal swab, moistened with broth, was taken on admission or as soon after as possible.

At operation the surgeon or assistant added to the form the date and certain other details required for the Public Health Laboratory Service survey, i.e., type of operation, time taken, length of incision, and a forecast of the number of days he expected the patient to remain in hospital if the wound healed by first intention and recovery was uneventful. He also added the type of skin antiseptic applied before operation.

A swab, moistened with broth, was taken of the wound at first dressing, every few days if the wound was septic, and a final swab just before discharge. When the patient left hospital the date of discharge was recorded and a note made of the state of the wound. Four variations were noted: (1) Clean. (2) Clean but infected, i.e., a perfectly clean wound yet pathogens isolated on swabbing. (3) Septic but not infected, i.e., a septic wound but no pathogens isolated. (4) Septic and infected, i.e., the wound showing one of the major signs of sepsis and a pathogen isolated. Records of wound swabs and the state of the wound with the organisms isolated were made on the reverse side of the form.

The skin antiseptic applied before operation was one of four in common use in both hospitals and in each case was the one with which the surgeon had been accustomed to work for many years. These antiseptics were:—

1. Cetavlon + watery cetavlon, i.e., an application of cetavlon ½ per cent in alcohol 65·6 per cent followed in 30 sec. or so by a wash of cetavlon 1 per cent in water.

2. Spirit—Industrial methylated spirit (95 per cent alcohol).

3. Euflavine—Euflavine 1 per cent in spirit (70 per cent alcohol).

4. Cetavlon—Cetavlon ½ per cent in alcohol (65·5 per cent).

It was apparent soon after the study began that fallacies would appear when analysing the results and assessing the value of the skin antiseptics as a means of preventing sepsis. Two surgeons used one type of preparation, euflavine in spirit, in one hospital, one surgeon in the other hospital used cetavlon in spirit followed by watery cetavlon, and the fourth used cetavlon in spirit alone. With this in view, therefore, all surgeons were asked to use iodine 2 per cent in spirit (70 per cent alcohol) for certain periods so that the results with iodine could be compared with those when using their normal choice of antiseptic. From April 1, 1958, to March, 1959, it was agreed that each surgeon should use iodine for the same fortnight in every month and his usual antiseptic for the remaining fortnight. Iodine and non-iodine sessions therefore were organized simultaneously in both hospitals and the scheme worked reasonably well. A calendar was prepared for a year from the date of commencement of the scheme so that the theatre staffs in both hospitals were aware of what was going on, the pharmacists had similar time tables, stocks of freshly prepared iodine were always supplied to the theatres before the sessions began, and a surgeon had no need to remember when a session was due to begin or end, the theatre staff automatically arranging this for him.

There were one or two difficulties. One surgeon disliked using the cautery where a spirit lotion had been applied and preferred to wash over the area with watery cetavlon some 30 or 45 sec. after the application of iodine. Another insisted on using industrial spirit on malignant breasts likely to have X-ray therapy later and in operations on varicose veins; but with these exceptions the sessions were well maintained and the routine followed.

As regards examination of the surgeons' gloves, the method adopted was for the surgeon to strip off his gloves and put them in a sterile dish, which was then brought to the laboratory. Swabs moistened with broth were rubbed on the inside of the gloves and the swabs broken off into 10 ml. quantities of 6 per cent salt broth. It was felt that dilution in this amount of broth would help to neutralize any antibacterial effect of the powder in the gloves. This procedure was abandoned after a time and an easier and more precise method was used. With this the author went to the operating theatre and swabbed the gloves of the surgeon, the assistant, and occasionally the theatre sister or nurse. The surgeon would first pull off one glove as far as the fingers, exposing the palm of one hand and the inside surface of the glove. A broth-moistened swab was then rubbed over the palm, another over the inside of the glove, and two swabs were taken of the other palm and glove. Swabs were similarly taken of the other personnel involved, and on return to the laboratory the swabs were broken off into 10 ml. quantities of 6 per cent salt broth. This was cultured for 48 hours, and subculture then made on to blood-agar plates. Some swabs were also taken towards the end of the study of the gloves of one of the surgeons and a sister after the use of phisohex for scrubbing up. It had been found that the hands of these two were frequently contaminated with *Staphylococcus aureus*.

Blanket contamination was studied by using the method originally described by Blowers and Wallace

(1955), and sweep plates were made of the top blankets of all beds in eleven wards of the two hospitals, surgical, orthopædic, surgical convalescent, and three medical wards for comparison. An attempt was made to carry out the same number of sweeps on each blanket with the sweeps following the same pattern. This was not always possible, for example, if a cradle covered a limb under the blanket; nevertheless, the sweeps were kept as uniform as possible. Some mattresses in each ward were also examined by sweep plates. Three surveys were made of the blankets of the wards mentioned. The first was in February, 1959, before any attempt was made to sterilize. The second was in May, 1959, after the 'lissapol cirrasol' process had been in operation in Hospital A for two and a half months and a commercial laundry using arquad had been sterilizing the blankets of Hospital B. The third was in October, 1959, when the sterilizing process was well established in both hospitals and blankets were being sterilized on discharge of every patient or after every three weeks for long-stay patients.

Table I.—Total Operations showing relation of Sepsis to Antiseptic Used

Total Operations		Cetavlon + Watery Cetavlon	Spirit	Euflavine	Cetavlon	Iodine + Watery Cetavlon	Iodine
Total	1811	581	110	504	173	170	273
Septic and infected	230	61	28	54	29	21	37
Percentage	12·7	10·5	25·4	10·7	16·7	12·3	13·1

Table II.—Lighter Type of Operation showing relation of Sepsis to Antiseptic Used

Antiseptic	Appendix		Hernia		Varicose Veins		Orthopædic	
	A	B	A	B	A	B	A	B
Cetavlon + watery cetavlon	101	11 (11)*	96	8 (8)*	37	1 (3)*	27	—
Spirit					30	7 (23)		
Euflavine	129	12 (9)	120	4 (3)	19	1 (5)	1	—
Cetavlon	54	5	18	1 (5)	6	2 (32)	45	2 (4)
Iodine + watery cetavlon	29	3 (10)	26	4 (15)	26	1	4	—
Iodine	69	12 (7)	47	3 (6)	14	3 (21)	16	—
Total	382	43 (12)	312	20 (6·4)	132	15 (11)	93	2 (2)

A, Total operations of one type using different antiseptics.
B, Numbers septic infected with percentage B of A.
* Figures in brackets indicate per cent.

For the air-contamination studies the author was fortunate in being able to call on Dr. R. E. O. Williams, Director of the Air Hygiene Laboratory at the Central Public Health Laboratory, Colindale. Using a slit sampler from the Air Hygiene Laboratory, Dr. Williams made observations lasting for three hours each during operating sessions in both hospitals and routine working in surgical wards in both hospitals.

Table III.—Heavier Type of Operation showing relation of Sepsis to Antiseptic Used

Antiseptic	Gall-bladder		Gastrectomy		Other Abdominal		Others	
	A	B	A	B	A	B	A	B
Cetavlon + watery cetavlon	52	13 (26)*	43	16 (7)	81	11 (13)	44	7 (16)
Spirit							18	3 (17)
Euflavine	48	12 (22)	37	5 (13)	77	20 (25)	32	5 (16)
Cetavlon	13	1 (7)	12	1 (8)	17	5 (30)	12	1 (8)
Iodine + watery cetavlon	15	7 (46)	11	—	20	2 (10)	12	2 (16)
Iodine	17	4 (25)	27	3 (11)	46	7 (15)	14	3 (21)
Total	145	37 (25)	130	25 (19)	243	45 (14)	132	21 (16)

A, Total operations of one type using different antiseptics.
B, Numbers septic infected with percentage B of A.
* Figures in brackets indicate per cent.

RESULTS

Of the 1811 cases studied 230 (12·7 per cent) became septic and infected, i.e., either had general erythema, a stitch abscess, discharged serous fluid or pus, or broke down, and a pathogen (*Staph. aureus* in 70 per cent of cases) was isolated. These are related to the pre-operative antiseptics used as shown in *Table I*.

Table IV.—Effect of Iodine on Sepsis

Iodine or Iodine + Watery Cetavlon	No. of Operations	No. of Septic and Infected Wounds	Percentage
April 1–April 14, 1958	42	11	26·1
April 29–May 11, 1958	50	4	8·0
May 26–June 8, 1958	45	2	4·4
June 23–July 5, 1958	42	2	4·7
July 21–Aug. 3, 1958	0	0	
Sept. 15–Sept. 28, 1958	28	2	7·1
Oct. 13–Oct. 26, 1958	49	5	10·2
Nov. 10–Nov. 23, 1958	46	9	19·5
Dec. 8–Dec. 21, 1958	36	6	16·6
Jan. 4–Jan. 17, 1959	59	8	13·5
Feb. 2–Feb. 15, 1959	42	4	9·5
Total	439	53	12·0
Non-iodine Sessions			
April 15–April 28, 1958	65	8	12·3
May 12–May 25, 1958	41	4	19·7
June 9–June 22, 1958	55	5	9·0
July 7–July 20, 1958	38	2	5·2
Sept. 1–Sept. 14, 1958	6	0	
Sept. 29–Oct. 12, 1958	37	1	2·7
Oct. 27–Nov. 9, 1958	55	8	14·5
Nov. 24–Dec. 7, 1958	54	10	18·5
Dec. 22, 1958–Jan. 3, 1959	36	2	5·5
Jan. 18–Feb. 1, 1959	54	3	5·5
Feb. 16–March 5, 1959	59	2	13·5
Total	500	45	10·2

Of the six antiseptics only iodine or iodine + watery cetavlon was used by all four surgeons. The other antiseptics represent the work of individual surgeons and the rates for cetavlon + watery cetavlon, euflavine, iodine + watery cetavlon, and iodine do not differ greatly from the overall sepsis rate. The figures for spirit are derived from fewer operations, and of these a large number were major operations in elderly people and therefore especially liable to sepsis.

Table II displays the lighter type of operation showing relation of sepsis to antiseptic used and *Table III* the heavier type of operation. In these two tables, where a breakdown of the numbers of operations into types is made, it is evident that there is a good deal of irregular variation in the sepsis rate in different types of operation and with different antiseptics. No doubt a good deal of the variation was due to the small numbers of operations, as for example, varicose veins following cetavlon or iodine and gall-bladders following iodine + watery cetavlon. In addition, in the figures for appendicitis, those cases where an abscess was found at operation were included, and it is difficult to imagine any particular antiseptic preventing subsequent breakdown in the wound in these cases, but it is also evident that there is no skin antiseptic that is associated with results clearly and consistently better than others.

Table IV shows the effect of iodine on sepsis. Although a proportion of operations, such as radical mastectomies and Trendelenburg's operation for varicose veins, are not included because of the dislike of one surgeon of the use of iodine in these cases, the selection in the series is a wide one and covered practically the work of one year in the group hospital. After a bad start with a high percentage of septic cases from March 31, 1958, to April 13, 1958, it appeared for several months that iodine was effecting some improvement, but the rate soon levelled out and at the end of the series it was clear that the introduction of iodine had made no difference to the sepsis rate. Further, it could be said that the figures indicate that it does not matter whether iodine or one of the other skin antiseptics is used. This does not necessarily indicate that skin antisepsis in general is useless. After all, if these skin preparations are equally good one would not expect to find any difference in the sepsis arising after their use.

Table V.—Isolation of *Staph. aureus* from Surgeons' Gloves

Date	Surgeon	Swabs	Sterile	*Staph. aureus*	Micrococci	Others
Jan. 28–Nov. 2, 1959	Mr. B.	84	67	1	9	7
	Assistant W.	71	46	1	24	—
	Mr. C.	52	13	7	32	—
	Mr. D.	4	4	—	—	—
	Assistant S.	12	—	1	11	—
	Assistant V.	16	—	—	16	—
	Assistant T.	27	6	4	17	—
	Assistant X.	4	4	—	—	—
	Assistant P.	12	2	2	8	—
	Nurse Y.	12	4	4	4	—
	Mr. A.	27	1	14	12	—
	Assistant Q.	48	13	—	33	2
	Sister O.	20	3	7	10	—
	Sister L.	16	4	—	12	—
Total		405	167 (41)*	41 (10)*	188 (46)*	9
After Introduction of Phisohex Nov. 3–Nov. 27, 1959	Mr. A.	37	34	1	2	—
	Sister O.	16	15	—	1	—
	Sister L.	8	8	—	—	—
	Assistant Q.	4	4	—	—	—
Total		65	61 (93)*	1	3	—

* Figures in brackets indicate per cent.

Table V shows the isolation of *Staph. aureus* from surgeons' gloves. The numbers for the brief experiment when gloves were stripped off by the surgeons and sent down to the laboratory were too small to be of any value, but of 16 gloves examined none produced *Staph. aureus* and 10 gave non-pathogenic micrococci.

Table VI.—TOTAL TOP BLANKETS YIELDING *Staph. aureus*

SURVEY	DATE	TOTAL BEDS IN 11 WARDS	TOTAL TOP BLANKETS YIELDING *Staph. aureus*
1	Feb., 1959	257	148 (54)*
2	May, 1959	257	121 (47)*
3	Oct., 1959	257	118 (45·9)*

* Figures in brackets indicate per cent.

general use in Hospital A, and the swabs were broken off into 10–12 ml. of broth to dilute any carry-over of powder into the broth. Other surgeons and assistants using the same kind of powder produced many gloves that were not sterile. What is interesting is that the two who produced far and away the largest number of sterile gloves were the only two who immersed and rinsed their hands and forearms in spirit after scrubbing up and then allowed the spirit to dry on their hands before powdering. This is the method described by Price (1951) and recommended by him as the best method of hand preparation before operation.

An extremely interesting change took place when Surgeon A., Sister O., Sister L., and Assistant Q. agreed to try phisohex instead of soap when preparing for operations; 93 per cent sterile gloves resulted and *Staph. aureus* was isolated only once.

Although Smylie, Webster, and Bruce (1959) used tween 80 to neutralize any phisohex carried over on to plates in his glove-contamination experiments, it was felt that dilution of the swab in large amounts of broth would probably be sufficient to reduce the amount of

Table VII.—CONTAMINATION OF MATTRESSES

WARD	DATE OF SAMPLING	MATTRESSES YIELDING *Staph. aureus*	PREDOMINATING PHAGE TYPES
1	May 15, 1959	0/2	—
	Oct. 28, 1959	0/3	—
2	May 15, 1959	1/2	N.T. (1)
	Oct. 21, 1959	1/3	80 + (1)
3	May 21, 1959	1/3	80 + (1)
	Oct. 20, 1959	0/3	—
4	May 22, 1959	0/1	—
	Oct. 18, 1959	2/4	70 + (2)
5	May 15, 1959	1/3	75 + (1)
	Oct. 19, 1959	2/4	80 + (2)
6	Oct. 26, 1959	0/4	—
7	May 13, 1959	3/3	52/52A/80 (1) 52/80 + (52A) (1)
	Oct. 12, 1959	1/3	80 + (1)
8	May 11, 1959	2/2	29/29 + (1) 80 + (52/52A) (1)
	Oct. 15, 1959	2/4	80 + (1) N.T. (1)
9	May 12, 1959	1/3	52A/79 (1)
	Oct. 16, 1959	1/3	80 + (1)
10	May 7, 1959	1/3	80 (1)
	Oct. 14, 1959	1/4	6/7/47/53/75/83 +
11	May 6, 1959	0/3	—
	Oct. 13, 1959	2/2	53 (1) 29/52 (1)

Table VIII.—AIR CONTAMINATION: THEATRE, HOSPITAL A

TIME STARTED	DURATION min.	CU. FT.	COUNT (Col. per cu. ft.)		PHAGE TYPES PRESENT
			General	*Staph. aureus*	
9.54 a.m.	5	30	18	0·033	
10.14	10	60	17	0·033	
10.26	10	60	27	0·100	80 :2
11.07	10	60	23	0·067	6/7/47/53/54/75 :2
11.20	7	42	31	0·19	29/52/52A/79/80/54 + :1
11.27	7	42	15	0·048	
11.40	7	42	17	0	N.T. :1
11.53	7	42	16	0·024	
12.06 p.m.	7	42	12	0·048	
12.22	7	42	17	0·071	
12.38	7	42	32	0·071	
12.52	7	42	13	0·048	

The fact that one surgeon, Mr. B., and Assistant W. produced a large number of sterile gloves is noteworthy. The powder used as a glove lubricant was in

hexachlorophene carried over to negligible amounts. The amount of broth into which the swabs were broken off was increased to 15 ml. and sub-culture was made after 48 hours in case growth of staphylococci was slow.

Table VI details the examination of blankets. Blankets were found to be heavily contaminated with *Staph. aureus*, the top blanket usually giving most colonies on the sweep plates. In the surveys of February, 1959, and May, 1959, the commonest phage types were 52/52 A/80 or related patterns such as 52/80, but by October, 1959, the single 80 phage type constituted more than 80 per cent of the types found. A slight decrease, however, was apparent in the total numbers of blankets contaminated over the period.

Table VII deals with the contamination of mattresses. It is not generally appreciated that mattresses can harbour pathogenic organisms, but although the total number examined was relatively small it was clear that a large proportion were contaminated by *Staph. aureus* of the phage types found in infected wounds, type 80 and related patterns predominating.

Tables VIII, IX, X, and *XI* are concerned with the isolation of *Staph. aureus* from the air of the operating theatres and wards of both hospitals, using a slit sampler operated by the Air Hygiene Unit of the Central Public Health Laboratory, Colindale. The air contamination in both theatres and wards was heavy, and this is not surprising considering the amount of contamination present in the blankets and mattresses.

No significant decrease in the sepsis rate (*Table XII*) was noticed over the seventeen months covered by the study, the number of cases and the sepsis rate being strikingly constant. The table also disposes of the possibility of a seasonal element in the sepsis rate.

Table IX.—Air Contamination: Surgical Ward, Hospital A

Time Started	Duration min.	Cu. Ft.	Count (Col. per cu. ft.)		Phage Types Present	
			General	*Staph. aureus*		
10.30 a.m.	60	60	8·0	0·26		
10.30	60	60	9·2	0·29	80 +	:3
11.40	65	65	11·5	0·18	52/80 +	:2
11.40	65	65	8·8	0·18	N.T.	:3
12.45 p.m.	55	55	10·7	0·18		

Table X.—Air Contamination: Theatre, Hospital B

Time Started	Duration min.	Cu. Ft.	Count (Col. per cu. ft.)		Phage Types Present	
			General	*Staph. aureus*		
9.32 a.m.	7	42	30	0·071		
9.40	7	42	30	0·20 (?)	71	:4
9.52	7	42	21	0·19 (?)	80	:1
10.08	7	42	27	0·048	52/80	:1
10.20	7	42	35	0·048	53 +	:1
10·30	7	42	21	0·048	3C +	:1
10.41	7	42	19	0·095	N.T.	:2
10.51	7	42	17	0·048		
11.24	7	42	27	0·048		
11.41	7	42	26	0·071		
11.48	7	42	34	0·071		
11.54	7	42	36	0·071		

Table XI.—Air Contamination: Surgical Ward, Hospital B

Time Started	Duration min.	Cu. Ft.	Count (Col. per cu. ft.)		Phage Types Present
			General	*Staph. aureus*	
9.22 a.m.	60	60	15·5	0·29	
10.30	60	60	22	0·42	all 52/80
11.30	60	60	10·5	0·66	

DISCUSSION

Skin Antiseptics.—There is no doubt that in a study of this kind, when assessing the value of skin antiseptics, there are many possible fallacies to be considered. In the particular situation covered by this study there was considerable variation, for instance, in the conditions affecting the work of the four surgeons. Two of them worked principally in the theatre of one hospital; the other two did most of their work in the other hospital. At least, that was the accepted routine for list cases, although there was some interchange for emergencies. The theatres were different in design and surroundings and subjected to different degrees of air pollution. Although all four surgeons regularly carried out major operations,

the frequency of such operations, especially the heavier type of abdominal operations which usually carry a high incidence of infection, varied. One surgeon, for instance, had a preference for orthopædic work, and many of the operation wounds had no drain inserted and the wounds remained covered up until the time for removal of the stitches. There was naturally less of the abdominal type of surgery in his lists. Another had a preference for genito-urinary work, yet frequently operated on difficult thoracic cases. Yet another had a high total of gastrectomies or gall-bladder operations and also had rather more thyroidectomies than the average.

Table XII.—Quarterly Sepsis Rate

Period	Total Operations	No. Septic and Infected	Percentage	No. in Hospital*	Percentage
1957					
4th quarter	57	9	15·7	4	7
1958					
1st quarter	329	43	13	26	7·9
2nd quarter	327	40	12·2	17	5·1
3rd quarter	130	13	10	5	3·8
4th quarter	308	43	13·9	19	3·6
1959					
1st quarter	343	39	11	17	5
2nd quarter	327	43	13·1	19	5·8
	1811	230	12·7	107	5·9

* Numbers of cases remaining in hospital on account of sepsis at least 7 days over the surgeon's forecast.

As regards skin preparations, again there was variance; only two surgeons used the same antiseptic, but not for all cases, so that the introduction of iodine in regular sessions was viewed with interest, as at least one variable, the antiseptic, would be removed for regular periods. There was good reason for the choice of iodine. Gardner and Seddon (1946), Gardner (1948), Story (1952), and Colebrook (1941) all found that iodine 2 per cent in 70 per cent alcohol, iodine 1 per cent in 70 per cent alcohol, or iodine 2 per cent in watery 2 per cent pot. iodide were superior to other antiseptics in sterilizing the skin after suspensions of pathogenic organisms were applied. Harrison and Cruickshank (1952), after experiencing a 10–15 per cent sepsis rate in thoracic surgery over a 3-year period, achieved a dramatic fall to 3·7 per cent after changing from 1 in 1000 acriflavine in spirit to 1 per cent iodine in 70 per cent ethyl alcohol. Gardner was of the opinion that although the alcohol itself was a good sterilizer it was the iodine content of the application that was responsible for the permanency of the sterilization.

Examination of Gloves.—As regards gloves and possible contamination of wounds through puncture holes by staphylococci from the surgeons' hands, a good deal of work has been done. Devenish and Miles (1939) drew attention to the importance of glove puncture as a source of surgical infection, and Harrison and Cruickshank (1952) were satisfied that dipping the terminal phalanges in iodine before donning the gloves was an excellent method of reducing the infection of glove interiors. Webster (1958) found that the incidence of glove punctures in 1000 gloves was as high as 30 per cent, and showed that organisms readily passed from the operators' skin to the exterior of the glove, especially if the gloves were wet. More recently, Smylie, Webster, and Bruce (1959) showed that the use of phisohex was followed by a highly significant fall in the number of colonies of skin organisms grown from the finger pads of a surgical team at the end of operations. The results of *Table V* bear out the possibility of infection as a result of glove puncture, as staphylococci of the phage types causing wound infection were isolated on 10 per cent of occasions. In the study 14 persons engaged in operations, not necessarily performing the actual operation itself but handling instruments or taking part in such a way that infection could pass from hands to wounds, were examined over a period of 10 months. Judging by the frequency of isolation of *Staph. aureus* 2 were a distinct danger, 2 were relatively harmless, and the remainder were somewhere between the two extremes. It could be said, therefore, that it would be beneficial for a surgeon to have a study made of the flora carried on his hands after operations lasting for an hour or more, and for those who produce *Staph. aureus* regularly and abundantly there is a remedy in applications such as phisohex. This is a procedure that instinctively one feels should be beneficial, but it is interesting to note that two heavy carriers worked together in one theatre and the two lightest carriers in the other, and the sepsis figures were practically the same in both hospitals. On the other hand, the fact cannot be disregarded that the strains of *Staph. aureus* isolated from the hands of one of the heavy carriers were identical with the strains appearing in infected wounds. Some other interesting facts emerge from the study. Mr. B. did not appear to carry *Staph. aureus* on his hands in even small numbers; in fact, even micrococci only rarely appeared and his hands were sterile on 67 (80 per cent) occasions after operations lasting an hour or more. Mr. C., on the other hand, was not so fortunate, and could finish his operation with sterile hands on only 13 (23 per cent) occasions. Micrococci were isolated frequently, 32 (61 per cent) occasions, but *Staph. aureus* turned up on at least 7 (13 per cent) occasions.

Considering Mr. A. we find that his hands yielded staphylococci frequently. He could only finish with sterile hands on 1 (3·7 per cent) occasion, non-pathogenic staphylococci appeared on 12 (44 per cent), and *Staph. aureus* often, on 14 (55 per cent) occasions.

The assistants produced fair numbers of sterile gloves, 75 (37 per cent) between them. *Staph. aureus*

appeared in only 8 (4 per cent) operations, but other staphylococci were isolated frequently, 109 (57 per cent) occasions. Of the two theatre sisters studied, one produced *Staph. aureus* frequently, 8 (35 per cent) occasions, the other not at all.

From this investigation, therefore, it would appear that some surgeons, assistants, sisters, or nurses are in the fortunate position of not carrying *Staph. aureus* on their hands, at least in sufficient numbers to be picked up on swabbing. Mr. B., for instance, only produced *Staph. aureus* on 1 occasion out of 84 swabs. Assistant W. similarly produced *Staph. aureus* only once, but Mr. A. and Sister O. appeared to be regular and abundant carriers of *Staph. aureus*. The phage types produced by these two were as follows:—

		Occasions
Mr. A.	80 + (52/52A)	3
	52/80 +	3
	52 A	2
	52A/79	1
	80 +	1
Sister O.	7/42 Ew	4

Contamination of Blankets.—The next factor to be studied was contamination of blankets and the effect on the sepsis rate, and this was first taken up in February, 1959, when sweep plates were made of the top blankets of all beds in 11 wards of the two hospitals, surgical, orthopædic, surgical-convalescent, and medical wards for comparison. Some mattresses were also examined. The first results, Feb. 20, 1959, to Feb. 23, 1959, showed that the blankets of 8 wards were heavily infected with the staphylococci being met with in wound sepsis, and those of 3 wards moderately infected. What was surprising was that the two medical wards were among the heaviest infected, 17 out of 25 and 23 out of 24 blankets respectively yielding many *Staph. aureus* on the sweep plates. The subject of blanket sterilization has been a very topical one during the past four years, and much work has been done on the sterilization of blankets and the substitution for wool of material that can be laundered easily. Blowers and Wallace (1955) and Blowers, Potter, and Wallace (1955) established the efficacy of quaternary ammonium compounds as sterilizing agents for woollen blankets and later showed how cotton or terylene substitutes were an improvement on wool. Schwabacher, Salisbury, and Fincham (1958) showed that when blankets were sterilized with quaternary compounds in a test ward the total bacterial count was reduced and cross-infection decreased, but that further improvement took place when cotton blankets were used. Caplan (1958) found that sterilization of blankets with formaldehyde was an economic and efficient method and, moreover, no shrinking or matting was observed in a period lasting over one year.

Hitherto in neither hospital had any special treatment been given to blankets; either they had been washed in the hospital laundry, or sent out, but a start was made in Hospital A with the 'lissapol cirrasol' process described by Blowers and Wallace (1955), and fortunately a commercial laundry was found locally that had already begun to use arquad for sterilizing blankets commercially. Those of Hospital B were sent to this laundry. Check tests of both methods were done and satisfactory results obtained. It was not possible to have blankets sterilized oftener than at discharge of a patient or every three weeks in a long-stay case, but every new admission was at least provided with sterile blankets. Following favourable reference to cotton substitutes it was agreed that replacements in future would be provided by purchases of cotton blankets. A second survey was carried out three months later on the same lines as the first, and judging the situation solely by the numbers of blankets yielding *Staph. aureus*, the position was worse in two wards, the same in one, and in eight some improvement had taken place. In many wards, however, a complete change of strain of *Staph. aureus* had taken place. Five months later a third survey was carried out and there is no doubt that results were disappointing. Some wards which had shown improvement at the second survey had gone back and there was certainly no obvious improvement. In fact, a widespread infection with phage type 80 was found to be present, and similarly no improvement had taken place in the hospital sepsis rate (*Table XII*). Again, changes in the ward phage type had taken place. For the last survey the mean number of colonies per blanket was estimated by dividing the total number of colonies of *Staph. aureus* on all the plates of one ward by the number of beds. Using this mean, a rough estimate could be made of the amount of infection in a ward and comparison was then possible between wards.

During the blanket checks it was noticed that the length of time the blanket had been on the bed bore little or no relation to the cleanliness. *Staph. aureus* was found in as little as 24 hours after putting clean blankets on a bed and this finding appears to be in keeping with observations of other investigators. Of the efficacy of the sterilization there was no doubt. Many blankets were examined after returning from either the hospital or commercial laundry and were always found to be completely sterile, but there was equally no doubt that the interval between sterilizing was either too long or the source of infection in the wards too great.

Although no improvement in the sepsis rate resulted from sterilization of the blankets it is not considered that the procedure is valueless. It is true that *Staph. aureus* appeared on some blankets within 24 hours, but the general impression gained was that the amount of infection, or total numbers of staphylococci, was rather less than before the beginning of the sterilization procedures. The mean count was of some help in arriving at this conclusion and will be used in future surveys to estimate progress. In a way the complete change of strains in a ward also helped to form the impression of a lessening of the colonization, at least it pointed to the complete removal of large depots of other strains; and although sterilization does not prevent rapid colonization by a new strain, it at least prevents a gradual build-up of many strains. It was noticed, by using the mean count, that on occasions infection of a blanket was represented by a single colony. It is reasonable to assume, therefore, that regular sterilization of blankets must have some beneficial effect.

Air Pollution.—The final factor to be investigated was that of air pollution in the operating

theatres of both hospitals, and the figures obtained on sampling showed heavy contamination by *Staph. aureus*. In Hospital A it will be possible to increase the pressure of incoming filtered air until it is positive, but in Hospital B a new ventilation system is necessary and must await funds. It is interesting to note that Kinmonth, Hare, Tracy, Thomas, Marsh, and Jantet (1958) found no improvement in the sepsis rate after the introduction of a cross-draught of fresh filtered air into a theatre and directed across the table. On the other hand, Lowbury (1954) reviewing the results obtained by Bourdillon and Colebrook (1946) and his own when treating burns in a special dressing room, air-conditioned and with an air filter, was able to point to considerable improvement in the sepsis rate under these special conditions. Shooter, Taylor, Ellis, and Ross (1956) found that when a powerful input stream of pure air was directed across the operating table and a positive pressure obtained, the bacterial content of the air in the operating room was greatly reduced and the sepsis rate fell from 9 to 1 per cent. Hare and Thomas (1956) also pointed to the probability of the air being contaminated from the clothing of personnel in the theatre, and in the absence of proof to the contrary, the possibility must be accepted of a part at least of the wound sepsis being due to infection in the theatre.

This discussion would not be complete without the question being asked that if such measures as blanket sterilization or the introduction of iodine have little or no effect on the sepsis rate, or if having septic hands or clean hands similarly appears to bear no relation to it, then what is the answer to this problem? One feels that there can be no hope of any individual measure being of value so long as the depots of sepsis, the patients themselves, are allowed to remain in the wards. If septic cases discharging pus carrying large numbers of *Staph. aureus* are allowed to remain in wards the build-up of these organisms is so heavy that they spread to every quarter of the hospital including the operation theatres. The answer must be surely one of prompt and effective isolation, whether it be through the provision of a septic block, or cubicles with effective air ventilation, or removal of the patient to an isolation hospital; only then can subsidiary measures be expected to assist in producing good results.

SUMMARY

1. In two hospitals of a provincial town in England, in 1811 operations studied from September, 1957, to June, 1959, a post-operative sepsis rate of 12·7 per cent was found. Virtually 70 per cent of the sepsis was due to infection with *Staph. aureus*.

2. Of four pre-operation skin antiseptics used, no one antiseptic appeared better than any other in preventing post-operation sepsis. After the introduction of iodine 2 per cent in 70 per cent alcohol in regular sessions no improvement in the sepsis rate was observed.

3. The institution of blanket sterilization by either the lissapol cirrasol or the arquad process on discharge of a patient, the issue of sterile blankets to new cases, and 3-weekly sterilizing of blankets for long-stay cases had no effect on the sepsis rate. Regular sterilization did, however, appear to reduce the amount of contamination in blankets.

4. Swabs taken of the hands of the four surgeons and of ten other persons concerned in operations showed that after operations lasting an hour or more, two, a surgeon and an assistant, rarely produced *Staph. aureus*, two, a surgeon and a sister, were regular carriers of *Staph. aureus*, and the remainder not infrequently carried *Staph. aureus*. The use of phisohex for the heavy carriers resulted in virtually sterile hands. It was not possible to carry on with the use of phisohex for long enough to see if any change took place in the sepsis rate.

5. The air in both theatres was heavily contaminated by *Staph. aureus*. It is reasonable to assume that this was one of the factors responsible for the sepsis rate.

6. It is concluded that no procedure to deal with the sepsis rate can be expected to be of any value as long as septic cases are allowed to remain in hospital wards, and that prompt and effective isolation must be the first of any measures adopted.

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CORD MOVEMENTS AFTER THYROIDECTOMY

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During the five-year period Jan. 1, 1955, to Dec. 31, 1959, an opportunity presented itself to study 250 consecutive patients subjected to thyroidectomy by one of us (G. B.). All were laryngoscoped before and after operation with a view to assessing cord movements, the incidence of recurrent nerve injury, and the effect, when it occurred, on laryngeal function.

The laryngoscopic examinations were carried out in the Ear, Nose, and Throat Department. At the time of the post-operative laryngoscopy, observations made during the operation by the surgeon or anæsthetist were unknown to the laryngologist. In this way it was hoped to collect unbiased observations in a consecutive series of cases large enough to permit some deductions about the value of exposure of the recurrent laryngeal nerve on both sides as a routine in the performance of thyroidectomy.

ANALYSIS OF CASES

Of the 250 cases, 213 were female and 37 male. In 5 the diagnosis proved to be carcinoma (2 male and 3 female); one of these presented with a paralysed right cord, which was unchanged after thyroidectomy.

Unilateral cord paralysis occurred post-operatively in 9 cases, 5 of which proved permanent and 4 temporary. Three of the 4 temporary paralyses recovered in 2 months or less. There was no case of bilateral paralysis.

Table I.—Thyroidectomies
(250 *cases*)

5 Carcinoma (2 male, 3 female)	245	Nodular Goitre
		Primary or Secondary Thyrotoxicosis (35 male, 210 female)

Table II.—Recurrent Nerve Paralysis after Thyroidectomy
(250 *cases*)

5 Permanent	3 Right, 2 Left (1 male, 4 female)	4 Temporary	1 Right, 3 Left (2 male, 2 female)
	No recovery at 3 mth. or longer		3 recovered in 8 wk. or less

The laryngoscopy proved very difficult in 1 patient included in the list of permanent paralyses. Such an imperfect view of the cords was obtained that it was impossible to decide, even after 6 examinations, whether the larynx was normal. The impression was that the right cord was paralysed and that it remained so when the patient was last seen 3 months after operation.

It is also of note that 2 of the 250 patients required re-exploration of the neck for hæmatoma within 3 days of operation but cord movements remained normal in both in spite of this.

Operative Findings.—The recurrent nerve was invariably exposed on each side and the inferior thyroid artery divided. Observations of previous workers were confirmed in respect of extraglandular branching of the nerve being the rule and 2 or 3 branches the common number. No instance was found of the nerve traversing the gland substance, and the claims of Armstrong and Hinton (1951) and Berlin (1935) that this occurs could not be substantiated. The close relationship of the nerve to the suspensory or lateral ligament and the varying relation to the inferior thyroid artery and its branches, described in many papers, were found in this series of cases also. One aberrant right nerve was found passing from the vagus obliquely into the tracheo-œsophageal groove without being recurrent. Absence of the inferior thyroid artery was also encountered rarely (Bowden, 1956).

Of the factors exposing the nerve to risk or protecting it, the height of the thyroid gland appeared the most important. When the gland was in a position with the isthmus in front of the cricoid cartilage, as occurred not infrequently, injury to the nerve at the lower border of the inferior constrictor muscle of the pharynx appeared less likely than when the anatomy was orthodox. It was also seen that the nerve was more liable to trauma when there was retrotracheal or retrosternal extension of the gland.

Although the slightly more exposed and superficial position of the right recurrent nerve has repeatedly been stated in the literature as the reason for more frequent injury on that side, this has not been confirmed in the series under examination.

A previous operation on the thyroid gland was the most important factor rendering exposure of the nerve difficult, but it never precluded it.

One of the patients had a hæmatoma within the sheath of the recurrent nerve visible at and due to operation. This hæmatoma was a few millimetres in size only and was not due to known trauma from an instrument, as it was an invariable rule that the nerve should never be handled or touched in exposing it. The post-operative laryngoscopy showed the corresponding cord to be completely paralysed, recovery taking 8 weeks (Judd, New, and Mann, 1918).

Anæsthesia.—Hypotensive drugs have not been used and avertin has been employed frequently as premedication.

Endotracheal anæsthesia was the rule and no significant difference was observed between the use of a cuffed and non-cuffed tube. A predilection for the latter seemed natural in the first instance, but experience showed that the risk of tracheal sloughing after the employment of a cuff on the tube was theoretical rather than real. In no case, moreover, was any limitation of cord movement ascribed to intubation.

Laryngoscopy at the end of operation is in our view unreliable, and inferences about cord movements at this time may be misleading. Relaxants and the tube itself are the obvious factors during operation which make cord movements difficult to appraise.

In fact the laryngological observations have been made in the first instance 3–5 days after thyroidectomy and repeated only when some abnormality was noted.

Various lesions of the larynx thought to be related to intubation were observed, as follows:—

1. A granuloma over the vocal processes 5
2. A superficial slough or ulcer over the vocal processes 5
3. A superficial slough or ulcer in the interarytenoid region 2
4. A superficial slough or ulcer of the front wall of the trachea below the larynx 1
5. Subglottic œdema 1
   (This condition necessitated tracheostomy)

Further reference to these lesions is made below, in the paragraph dealing with hoarseness. Laryngeal movements were not seen to be affected in any of these cases. This is not in accordance with the observations of Ross and Sukes (1957).

Laryngoscopy.—The examination was carried out by the indirect method and a satisfactory view usually obtained without resorting to surface anæsthesia.

A total of 532 laryngoscopies was performed. In the 42 cases where gagging and retching created difficulty, decicaine lozenges were employed 6 times, but it is interesting to note of what little value this form of surface anæsthesia proved. The afferent nerves concerned in this reflex are not only the 9th and 10th nerves, because this type of patient will often commence to gag when asked to open the mouth and before an instrument is introduced. Gross distortion of the larynx by a large nodular goitre was found to make assessment of symmetrical cord movements difficult in 2 or 3 cases, and in 1 case, in which a gland weighing 900 g. was removed, distortion of the larynx completely prevented pre-operative examination of cord movements.

An additional difficulty was encountered in the post-operative examination. The ideal position of the head for laryngoscopy is with the neck flexed and the head extended. The position stretches the skin of the front of the neck and the patient is most reluctant to assume it immediately after thyroidectomy. On several occasions it was necessary to postpone the post-operative examination for a day or two in order to diminish this difficulty.

Fortunately it is possible to assess movement of the vocal cords without visualizing the anterior commissure or indeed the major part of the cord at all. Observation of the movements of the arytenoid cartilages, particularly the movement of the vocal processes, is sufficient in the difficult case. If it had not been for this there would have been a greater number of failures. As it was, it was necessary to confess failure to observe the larynx well enough to report with certainty on the movements in only 14 cases. It was not justifiable, in our opinion, to propose direct examination in these cases.

An unexpected problem facing the laryngologist in this survey needs mentioning. The exact purpose of the laryngeal examination could not be explained to the patient except in general terms, for fear of creating unnecessary anxiety. When several post-operative examinations were demanded in the paralysed cases this problem assumed important proportions. In one case it was discovered after several examinations that the patient supposed that we suspected her of having cancer of the throat. No further laryngoscopy was undertaken and it is hoped that our strong reassurance dispelled the patient's fear.

As would be expected, among the 250 cases concerned there came to light a certain number of examples of laryngeal disease not related to the goitre or to the operation. There were 4 of these, all discovered before the operation and found to be unchanged after it. They included 3 cases in which the mucous membrane over the cord or cords had undergone a polypoid change, localized in 1 case, generalized in the other 2, and 1 case of subglottic stenosis, the cause of which was not ascertained.

At the commencement of the study it was decided that as a secondary objective the opportunity should be taken of observing the application of Semon's law to the paralysed cases. Fortunately the number of these was not great enough to provide much scope for this, but two points should be mentioned, although a full discussion of this aspect of the problem is out of place here.

In cases of unilateral paralysis a decision as to the position of the paralysed cord in relationship to the midline is not always easily reached. This is particularly true if the larynx is asymmetrical in other respects, and where there was a large goitre there was often considerable distortion, not always immediately corrected by operation. For example, one case was subjected to laryngoscopy on 11 occasions. The last examination was made 4 years after the operation. On each occasion the laryngologist recorded his observations before referring to the notes. Nine times the affected cord was thought to be immobile in the paramedian position, but on 2 occasions, at 1 year and 2 years after thyroidectomy, it was considered to be in the midline. In another case, of 5 observations made, 4 were recorded as showing the cord in the midline position but at the third examination the cord was thought to be in the paramedian position.

If these discrepancies are ignored, the position of the paralysed cord was paramedian in 8 cases and midline in one.

Hoarseness as an Indication of Nerve Injury.—It was the exception rather than the rule for the voice to be normal for a day or two after operation, the fact being that intubation, however skilfully performed, usually produces some degree of huskiness or weakness of the voice. Particularly is this so when the tube is lubricated before insertion with an analgesic ointment, such as amethocaine (2 per cent cream).

A few patients continued to complain of different varieties of dysphonia for longer than a day or two, but it was shown that there was no constant relationship between this and laryngeal paralysis. Sometimes the continuing hoarseness was due to some other laryngeal lesion, attributable to intubation but not affecting cord movements. Sometimes nothing could be seen to account for voice changes.

It is to be concluded, therefore, that hoarseness and weakness of the voice after thyroidectomy, far from indicating the presence of laryngeal paralysis,

is in the great majority of cases the result of some quite different lesion (Blackburn, 1958).

Can it be safely assumed that if the patient notices no alteration in voice after the operation the laryngeal nerves are intact and the laryngeal movements normal? That this inference, too, is not dependable was illustrated by 2 of our cases, each of whom 5 days after operation was found to have complete paralysis of one cord but, unlike the majority, claimed to have noticed no change in the voice.

Not one of the 5 cases remaining paralysed continued to complain of dysphonia after periods varying from 10 weeks to 6 months, and this is in accordance with the observed ability of the larynx to accommodate itself to unilateral cord palsy, the healthy cord coming in time to approximate itself accurately to the paralysed one.

DISCUSSION

That temporary and even permanent paralysis may be due to traction seems incontrovertible, and delivery of the lateral lobe into the wound by dislocation with the finger would appear to be the easiest way of producing this. Preference is therefore very marked for division of the pretracheal muscles in nodular goitre and in all thyroidectomies in men. With adequate retraction and deferment of sectioning the gland until all the main vessels have been divided, the risk of putting the nerve on the stretch is diminished; only retrosternal enlargement of any magnitude should then present much difficulty, and glands of this type are fortunately cystic and not vascular as a rule.

The vulnerability of the recurrent nerve, as Wade (1956) and others have stressed, appears to be greatest in the upper third of its course, and injury most likely at or just below the point where it enters the larynx in close relationship to the suspensory ligament of the gland. Lower down, where the nerve and inferior thyroid artery are closely related and where anatomical variations are common, it would appear imperative to expose both structures to ensure minimum risk. It must be emphasized, however, that this step, in our view, does not render post-operative laryngoscopy unnecessary, as Lahey (1944) claimed in the belief that the surgeon can guard against injury by so doing.

The superior laryngeal nerve, supplying the cricothyroideus muscle, has not shown evidence of damage in this series. Such injury may best be guarded against by detaching the superior thyroid vessels from the gland substance of the upper pole after clear definition of the interval between thyroid gland and larynx, leaving the laryngeal musculature intact.

CONCLUSIONS

1. A series of 250 consecutive thyroidectomies by one operator is analysed, with pre- and post-operative laryngoscopy in all patients.
2. There were 5 permanent and 4 temporary unilateral recurrent laryngeal nerve paralyses.
3. Superior laryngeal nerve paralysis was not seen.
4. Endotracheal anæsthesia with a cuffed or non-cuffed tube was the rule.
5. Assessment of cord movement by the anæsthetist at the end of operation is unreliable and of no real value.
6. Exposure of the recurrent nerves seems the best safeguard against injuring them.
7. The laryngologist—not the thyroidectomist or the patient—is the only person capable of recognizing or assessing recurrent laryngeal nerve injury.

Our thanks are due to Dr. A. M. Hutton and Dr. J. M. Hall, who anæsthetized the great majority of these patients, and to Mr. O. Shaheen, Registrar in the Ear, Nose, and Throat Department, who carried out a number of the laryngological examinations.

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INTRACRANIAL MENINGIOMATA ASSOCIATED WITH OTHER TUMOURS INVOLVING THE CENTRAL NERVOUS SYSTEM*

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INVOLVEMENT of the central nervous system by multiple neoplasms is not uncommon. Of such multiple growths, metastatic carcinomata occur with greatest frequency. In the central form of neurofibromatosis the nervous system may be involved by numerous neoplasms—gliomata as well as neurinomata and meningiomata. While intracranial neurinomata in this condition may arise on many of the cranial nerves, bilateral acoustic neurinomata are especially common and frequently associated with numerous meningeal tumours. The meningiomata occurring in central neurofibromatosis may be so numerous that Cushing (1938a) suggests the term 'meningiomatosis' for such cases to distinguish them from the group of cases in which multiple

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meningiomata occur in relatively small numbers with no associated neurofibromatosis. Cushing reports an incidence of the latter type of multiple meningiomata of only 3 cases in a series of 295. Other multiple tumours also involve the nervous system, and a cerebellar hæmangioblastoma may have

FIG. 411.—*Case* 1. Radiograph of sella turcica.

be of value in diagnosis and treatment, and in this paper the records of 4 patients with such tumours are presented. In each, an intracranial meningioma was associated with a tumour at a different site, and in 3 of the patients of different structure; in 2 of the patients the lesions presented simultaneously, and in 2 one lesion was followed by the other after an interval.

CASE REPORTS

Case 1.—M. H., housewife, aged 47 years. Admitted February 2, 1957, complaining of failing vision in her right eye.

HISTORY.—A year before admission she began to experience a recurring visual hallucination of a dazzling light before her right eye. Soon after this, right vision became misty and there appeared to be a central area of loss of vision in this eye, so that she could not read with it.

She had occasional frontal headaches but had never vomited, and she had no other symptoms of neurological significance. Her general health was excellent and there had been a weight gain of 7 lb. during the period of existence of her visual disturbance. There were no alimentary symptoms and no polyphagia, polydypsia, or polyuria. Menstruation had ceased three years previously, at 44 years. There was nothing relevant in the past or family history.

ON EXAMINATION.—The patient was an alert, intelligent woman, somewhat overweight. There was no

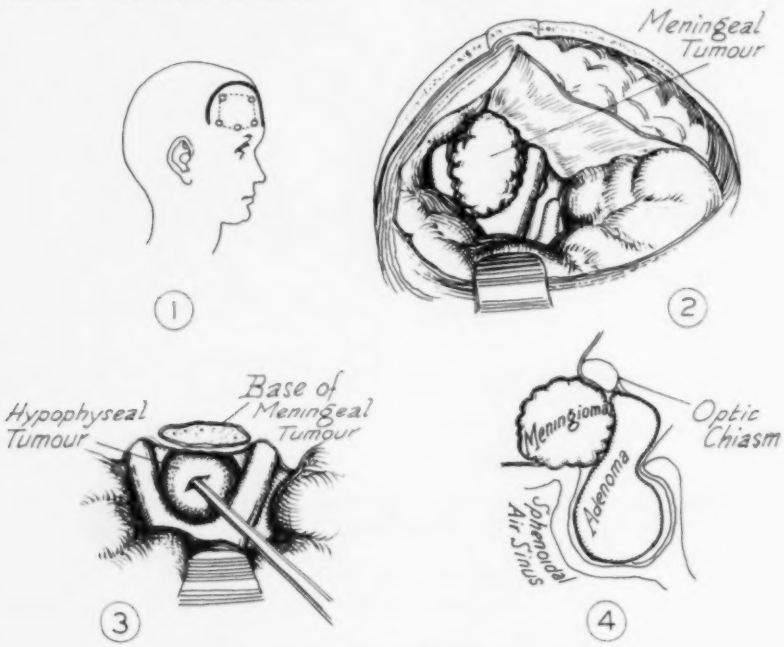


FIG. 412.—*Case* 1. Sketches of operative findings.

associated with it not only retinal hæmangioblastomata but one or more quite distinct tumours of identical structure in the cerebellum. Multiple primary gliomata are encountered infrequently.

Knowledge concerning the multiple tumours which may involve the central nervous system may

reduction of sense of smell, nor was there any neurological abnormality apart from the visual one. Ophthalmoscopy revealed a pale right disk with a clear margin and a normal left disk. The visual acuity was J.8 (corrected) on the right and J.1 (corrected) on the left. The field of vision of the left eye showed a defect in the upper temporal quadrant with the 3 mm. white test object, and almost a

temporal hemianopia with the 15 mm. red object. In the right eye a central scotoma spreading into the inferior temporal quadrant was revealed with the 5 mm. white test object; the fields for the smaller white and coloured objects were grossly reduced, being hemianopic with loss of central vision. General examination revealed no abnormality, the blood-pressure being 120/80 mm. Hg.

X-ray examination of the skull revealed a ballooning of the sella, with thinning of its dorsum and no other abnormality (*Fig.* 411).

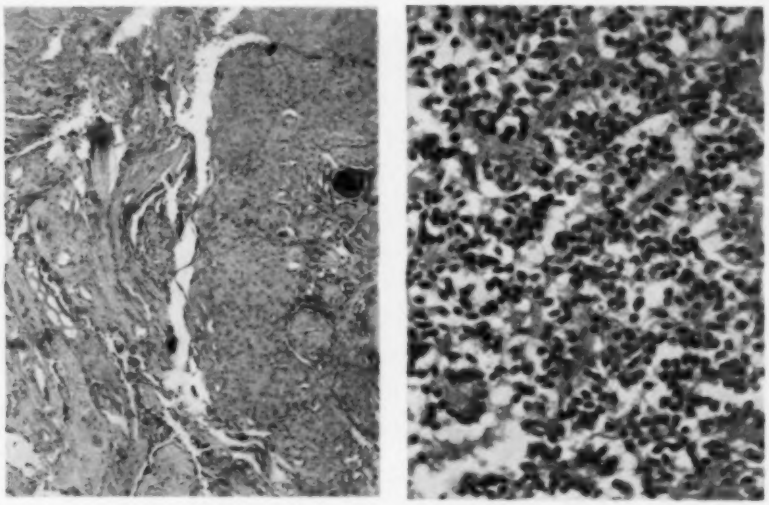
The basal metabolic rate was −25 per cent, the protein-bound iodine 3·8 μg. per 100 ml., and the glucose tolerance test showed a slightly flattened curve. 17-ketosteroid excretion was reduced to 2·2 mg. per day. A diagnosis of chromophobe adenoma of the pituitary was made.

AT OPERATION.—On Feb. 11 a small right frontal osteoplastic flap was turned down under general anæsthesia and an extradural approach to the chiasmatic region effected (*Fig.* 412). Elevation of the frontal lobe revealed a firm, pink, finely nodular tumour anterior to the chiasma and between the optic nerves—overlapping the right nerve on both its superior and inferior aspects. The mass was adherent to the dura mater at the tuberculum sellæ and was removed piecemeal, its base of attachment being subsequently cauterized. There was now revealed a smooth yellowish tumour mass projecting out of the sella turcica and extending posterior to the chiasma. Its capsule was incised and its contents removed by suction so that the capsule collapsed into the sella. Hæmostasis was secured and the wound was closed.

Histologically the anterior tumour was a meningioma of epithelioid type, showing whorl formation and some psammoma bodies (*Fig.* 413 A). The posterior tumour had the characteristic structure of a chromophobe pituitary adenoma (*Fig.* 413 B).

The patient was discharged three weeks after operation with already a considerable improvement of vision in the right eye. When last seen, twenty months after the procedure, she was free from symptoms and the visual acuity was J.1 bilaterally: the visual field on the left was normal and on the right showed only an inferior temporal quadrantic scotomatous defect.

In this patient the evidence of chiasmatic compression, hypopituitarism, and the radiological evidence of an intrasellar mass all pointed to the diagnosis of a chromophobe adenoma of the hypophysis. No abnormality of the region of the tuberculum sellæ was noted in the skull films pre-operatively, though examination of them at a later date suggested the possibility of some osteosclerosis at this point. The correct diagnosis would have been helpful since, while an extradural approach to the chiasmatic region is excellent for the removal of pituitary tumours, it may be inadequate for the excision of large, firm, vascular meningiomata.



A B

FIG. 413. *Case* 1. A, Section of meningioma. H. and E. (× 79.) B, Section of pituitary adenoma. H. and E. (× 262.)

Case 2.—J. K., male, a builder's labourer, aged 67 years, admitted March 10, 1950, complaining of loss of use of his legs.

HISTORY.—Four months before his admission he began to notice recurring feelings of constriction in his abdomen immediately below the umbilicus. Such sensations would last for an hour or two and recur once or twice daily. At the same time he began to have difficulty in mounting his bicycle, although he could ride it efficiently. Soon, however, he became aware of stiffness in his legs, with difficulty in rising from a sitting position and a tendency to stumble. Within three months of the appearance of his symptoms he could no longer work, and found walking increasingly difficult. In addition he was aware of a sensation of numbness in his feet. There was no disturbance of vesical or rectal control nor any other symptoms; neither was there anything relevant in his past or family history.

ON EXAMINATION.—The patient was an alert man, appearing a little older than his years, with marked sclerosis of his peripheral vessels, aortic incompetence, and a blood-pressure of 210/110 mm. Hg. General examination revealed as other abnormalities a considerable symmetrical enlargement of the prostate and a median thyroid nodule.

On neurological examination there was a severe spastic paraparesis, the left leg being more affected than the right and the lower abdominal muscles involved. Cutaneous sensibility was reduced below the 8th thoracic dermatome, postural sense being absent in the toes and vibration sense greatly reduced below the anterior superior

iliac spines. The abdominal reflexes were absent, the plantar responses extensor, and the knee- and ankle-jerks exaggerated, with sustained patellar and ankle clonus. There was no spinal deformity or tenderness and Naffziger's sign was negative. No abnormality was found on radiological examination of the spine or chest, and

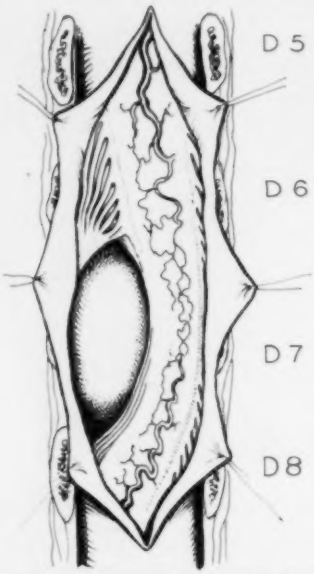


FIG. 414.—*Case* 2. Sketch of findings at laminectomy.

dorsal vertebræ were excised and on incision of the dura mater an ovoid tumour lying on the left posterolateral aspect of the cord was seen (*Fig.* 414). It was adherent to the theca at the foramina of exit of the 8th dorsal nerve on the left side. The mass was excised with sacrifice of this nerve and the wound closed in layers. The tumour

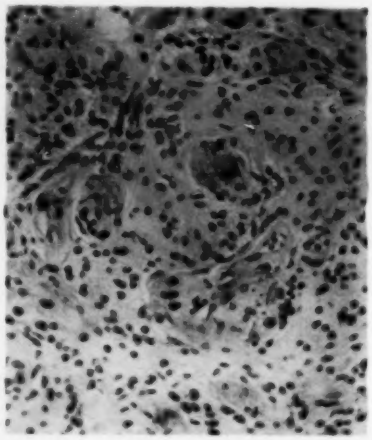


FIG. 415.—*Case* 2. Sections of spinal tumour. H. and E. (× 150.)

was 2·6 cm. long and 1 cm. in diameter, and histologically (*Fig.* 415) was a meningioma, showing characteristic vacuolated nuclei and some whorl formation.

FIG. 416.—*Case* 2. Radiograph of skull.

laboratory examinations of the blood and urine were negative, the E.S.R. and phosphatase concentrations being normal. Lumbar puncture revealed a complete subarachnoid block and produced a xanthochromic fluid containing 1·4 g. protein per 100 ml. A clinical diagnosis of spinal cord compression with its upper limit at the 8th dorsal segment was made. In view of the high protein concentration it was considered that a neurinoma was the likely cause of this compression. Myelography demonstrated a block at the level of the 8th thoracic vertebral body.

AT OPERATION.—On March 21, under general anæsthesia, the spines and laminæ of the 5th, 6th, 7th, and 8th

Post-operatively the patient made steady progress and was discharged, walking with a stick, after two months. Power was good, but spasticity, clonus, and extensor responses remained, although sensory disturbance faded to a mild reduction of posterior column conditions. He returned to his heavy work within a few months.

In July, 1951, sixteen months after his operation, the patient commenced to have attacks. In these, clonic movements of the right hand spreading to involve the leg and face occurred, continuing for periods of up to 2 hours, and being followed by a paresis of the right limbs for about 24 hours. They were sometimes preceded by

tingling in the right face, occurred every 5–6 weeks, and on only one occasion was there loss of consciousness with a generalized tonic phase and incontinence. In August, 1952, thirteen months from the onset of his cerebral symptoms a right hemiparesis appeared and progressed rapidly so that he was unable to walk and used his left hand for writing. In October, 1952, he was re-admitted to hospital and reported that he had had recent recurring urinary incontinence, and on one occasion had for some hours been unable to understand what was said to him, and at the same time his own speech had become a meaningless jargon. He had had a mild frontal headache for six months and considered that his vision had deteriorated.

Examination showed a mild degree of confusion, with a slight dysphasia involving both comprehension and expression. There was a well-marked spastic right hemiparesis and cortical hemihypoæsthesia, the visual fields, however, being full. There was no papillœdema. Electroencephalography showed a left parietal delta focus and skull films (*Fig.* 416) increased vascular markings in the same area, with a pineal displacement to the right. The C.S.F. protein was 150 mg. per cent and pneumoencephalography showed a left parietal mass (*Fig.* 417). Having confirmed that this was a meningioma, a bone-flap was made and a large globular parasagittal tumour excised (*Fig.* 418). Histologically the tumour was an epithelioid type of meningioma.

There was a transient post-operative hemiplegia, but at discharge, eight weeks post-operatively, the right-sided signs were greatly reduced and faded after two years to a mild spastic weakness of the right leg. He remained well until his death from cardiovascular disease at the age of

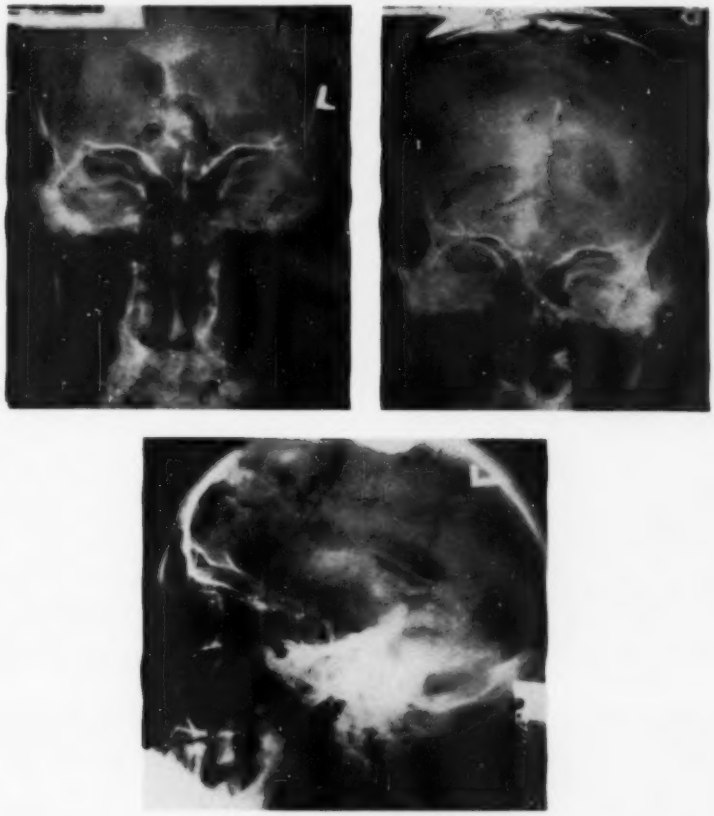


FIG. 417.—*Case* 2. Pneumoencephalogram.

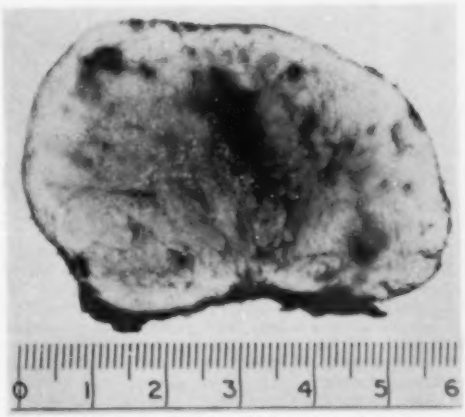


FIG. 418.—*Case* 2. Photograph of parasagittal tumour.

75, seven years after the excision of his spinal tumour and four and a half years after excision of the intracranial one.

The experience of this case serves to re-emphasize the importance of establishing the pathological nature of an intracranial lesion. Had this not been done, the patient's age and cardiovascular disease, as well as the severe focal neurological defect without evidence of raised intracranial pressure, might well have led to the conclusion that surgical treatment was not indicated.

Case 3.—R. M., male, window cleaner aged 41 years, admitted Oct. 13, 1948, complaining of headache and visual deterioration.

HISTORY.—Three months before his admission he began to suffer from headaches, frontal or occipital, and occasionally generalized. These were transient, recurring with increasing frequency, and were unassociated with nausea or vomiting. A month after the onset of the headache his vision began to fail in the left, and then in the right eye, the temporal visual fields being first involved on both sides. He had no other symptoms of nervous disease and his general health was good, there being no symptoms of endocrine deficiency. The past history contained nothing relevant. The patient was married with ten children, with an age range of 17 years to 1 year.

FIG. 419.—*Case* 3. Section of tumour. H. and E. (× 79.)

ON EXAMINATION.—The patient was a healthy looking man who showed no obesity and no alteration in skin texture or growth of hair. Although normally orientated with an adequate performance of the six digits and 100–7 tests, his responses were slow. There was no dysphasia. The abnormal neurological findings were: (1) A bilateral hyposmia, (2) A severe visual loss with appreciation of hand movements only on the left, the acuity on the right being 6/24, J.6. There was a bitemporal hemianopia and advanced atrophy of the left optic disk, with no evidence of papillœdema. (3) Dilated pupils reacting poorly to light, especially on the left. General examination revealed no abnormality. X-ray examination of the skull showed no enlargement of the sella turcica or any suprasellar calcification; there was a possible erosion of the tuberculum sellæ.

The clinical diagnosis of a chiasmatic compression, possibly due to a meningioma of the tuberculum sellæ, was made, and ventriculography performed. This revealed a left subfrontal tumour of considerable size, extending medially. (Unfortunately the films made at this patient's first admission had been destroyed before his later re-admission to hospital, and their reproduction is therefore impossible.)

AT OPERATION.—On Oct. 18 a large left frontal osteoplastic flap was elevated under general anæsthesia. Reflection of the dura exposed the wide and flattened convolutions of a tense frontal lobe and exploration with a cannula encountered a soft vascular area within the lobe. A frontal lobectomy was effected to reveal a soft vascular tumour. Much of this was removed by suction and a broad area of attachment to the dura mater anterior to the optic chiasma displayed, there being an intimate relationship between the tumour base and the left optic nerve and tract, as well as the left internal carotid artery. The relationships and vascularity of this portion of the growth were considered to contra-indicate attempts at its complete removal, and following hæmostasis the wound was closed.

Histological examination showed the tumour to be an angioblastic meningioma (*Fig.* 419). Post-operatively there was evidence of a considerable frontal-lobe defect, with apathy, double incontinence, and some confusion. However, he improved over a few weeks and he received X-radiation (4000 r) to the area of residual growth, with further improvement.

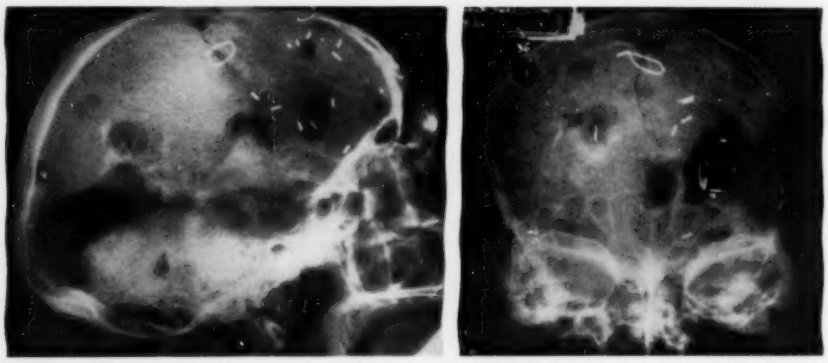


FIG. 420.—*Case* 3. Ventriculogram.

Subsequently he was seen every year for nine years. He showed evidence of a frontal lobe disturbance of moderate severity with a memory defect and some retardation. He was free from headache and his visual fields had enlarged considerably, although the visual acuity on the left remained greatly reduced. He had three attacks of unconsciousness soon after his treatment, but there was

no recurrence of these after the institution of anti-convulsive medication.

In May, 1958, nine years after the completion of treatment of the meningeal tumour, his condition began to deteriorate. He became increasingly confused, sometimes failing to recognize his family and going to bed without undressing. He was irritable and complained of headache, visual deterioration, and difficulty in walking. Following two attacks of unconsciousness accompanied by generalized convulsive movements, he was re-admitted to hospital on Aug. 5, 1958. He had lost much weight and was drowsy and disorientated in time and space. He co-operated in his examination but his attention was maintained with difficulty. The decompression was indrawn. The only other abnormalities were the previously noted well-marked atrophy of the left optic disk and a possible right central facial paresis. General examination was negative and laboratory investigations of blood and urine revealed no abnormality. Electro-encephalography revealed high-voltage, left, fronto-temporal delta activity. Skull films showed only the abnormalities occasioned by the previous operation. Left carotid angiography showed that the anterior cerebral artery was displaced to the left.

Ventriculography (*Fig.* 420) revealed a right parietal mass, some oxygen and thorotrast having been injected into the lesion at the same time as an aspiration biopsy was made. No further treatment was considered to be indicated as the aspirated tissue suggested the diagnosis of an astrocytoma, and the progression of the patient's dementia led to admission to a mental hospital, where he died four months after the re-appearance of the cerebral symptoms.

Section of the brain revealed an infiltrating tumour in the centrum ovale of the right hemisphere, with spread across the midline through the corpus callosum (*Fig.* 421). Histologically the tumour was a cellular astrocytoma, but lacked the pleomorphism characteristic of a glioblastoma (*Fig.* 422 A). A thin layer of meningiomatous tumour remained in the chiasmatic region. Histologically (*Fig.* 422 B) the tissue was less vascular and contained many more psammoma bodies than had the material excised ten years ago—a change which is probably attributable to irradiation.

In this patient, because of the incomplete removal of the original tumour and the absence of focal signs, the deterioration was thought to result from enlargement of the residual subfrontal meningioma, and only when angiography and ventriculography had revealed the right parietal mass was this diagnosis seen to be incorrect. The absence of focal signs and of evidence of intracranial hypertension was perhaps due to the internal decompression provided by the large left frontal lobectomy. The remote possibility that the parietal lesion was due to massive irradiation necrosis was considered, although the situation of the irradiated lesion made this a much less probable diagnosis than that of the glioma eventually found to be present.

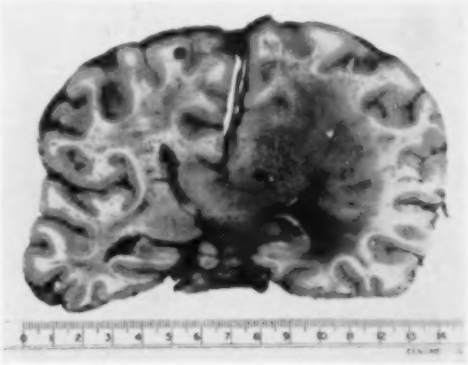
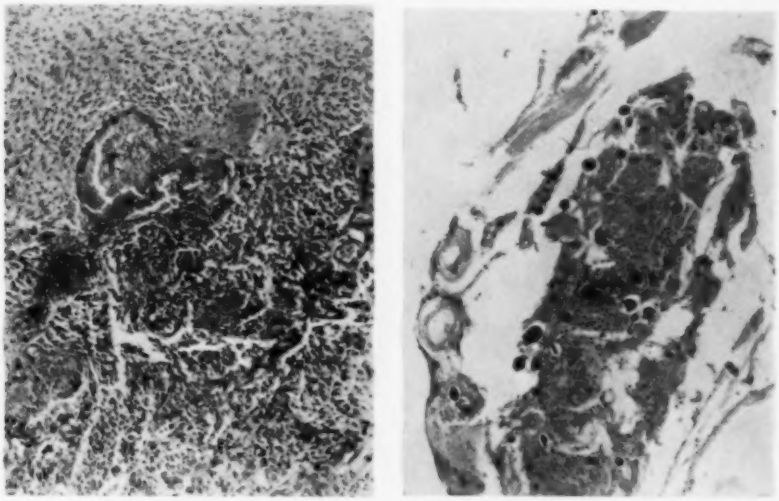


FIG. 421.—*Case* 3. Photograph of section of cerebrum.



A B

FIG. 422.—*Case* 3. A, Section of parietal tumour. H. and E. (× 79.) B, Section of residual meningioma. H. and E. (× 64.)

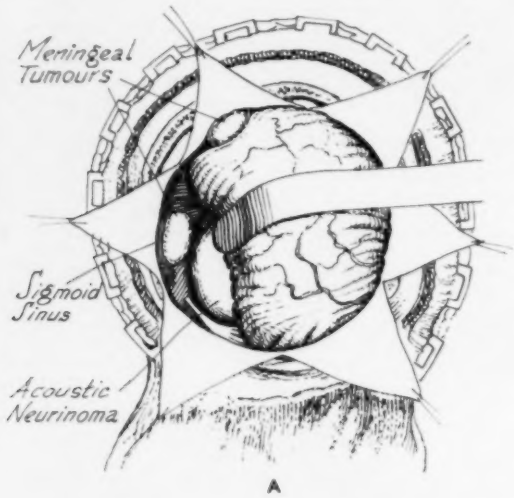
Case 4.—A. H., a female clerk, aged 18 years, admitted May 7, 1954, complaining of increasing deafness, headache, and unsteadiness of gait.

HISTORY.—Eighteen months previously a left deafness appeared, progressively increased, and was associated with a hissing left tinnitus. After six months hearing began to fail on the right side and at the same time frontal

headaches, worse in the morning, developed. For some months prior to admission there had been unsteadiness of gait. There was no vomiting, no dysphagia or dysarthria, and no subjective motor or sensory disturbance other than that of gait referred to above. She had no other symptoms.

FIG. 423.—*Case* 4. Radiograph of skull.

and lateral movements of the left eye. There was a horizontal nystagmus, coarser on deviation to the right. Sensibility was reduced in the territory of the ophthalmic division of the left 5th nerve, the corneal reflex being impaired. There was a mild peripheral facial paresis on



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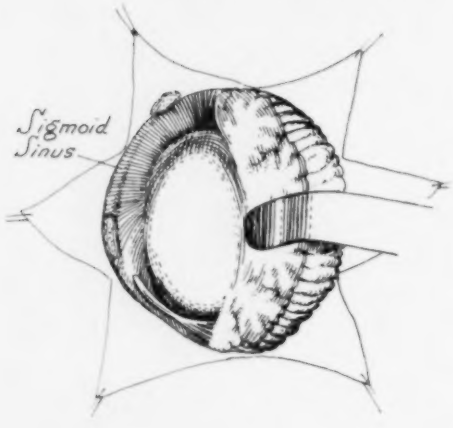

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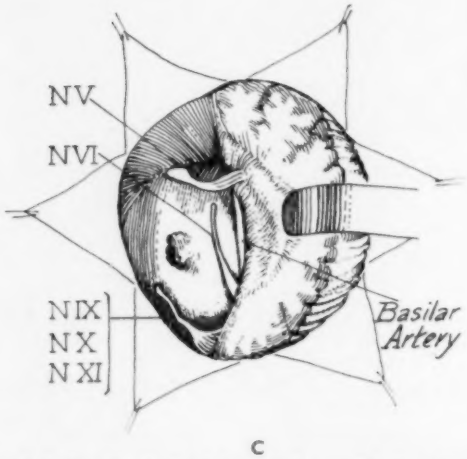

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FIG. 424.—*Case* 4. A, Operative sketch showing meningeal tumours. B, C, Operative sketches before and after removal of neurinoma.

In her past history the information that she had been born with a left internal squint emerged, and two attempts at its correction had failed. She was the eldest of five children, there being no family history of nervous disease.

ON EXAMINATION.—She was an alert co-operative girl who had overcome the disability occasioned by her deafness by learning to lip read expertly. There was no neck rigidity or skull tenderness. Examination of the cranial nerves showed a normal sense of smell and full visual fields. There was no papilloedema and the visual acuity was 6/6, J.1 on the right, being 6/18, J.6 on the left. This reduction of visual acuity on the left was associated with a congenital left internal squint and loss of upward

the left. There was total deafness on the left, with a considerable reduction of hearing on the right; similarly the labyrinthine response to caloric stimulation was absent on the left and reduced on the right. The other cranial nerves functioned normally. There was a mild ataxia of the left limbs, but no sensory or reflex disturbance. Romberg's sign was positive and the gait ataxic, with deviation to the left. On general examination the only abnormality was the presence of a few mollusca fibrosa on the trunk, as well as a number of small pigmented cutaneous spots. Radiographic examination of the skull showed erosion of the internal auditory meati, greater on the left side (*Fig.* 423). A diagnosis of

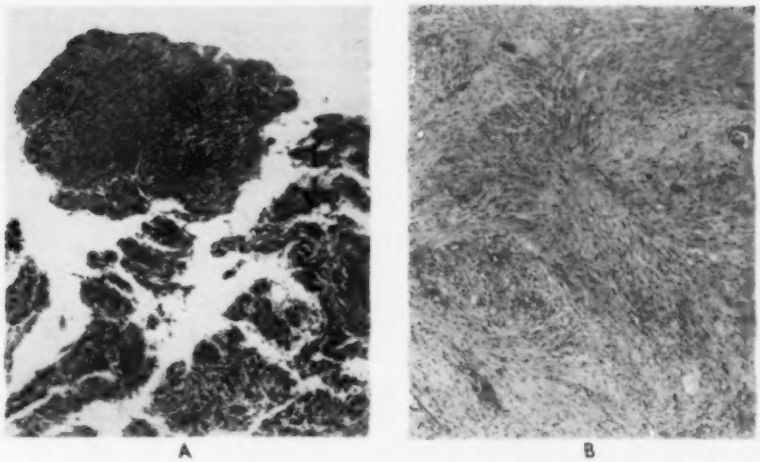

FIG. 425.—*Case* 4. A, Section of meningeal tumour. H. and E. (× 56.) B, Section of left cerebellopontine angle tumour. H. and E. (× 49.)

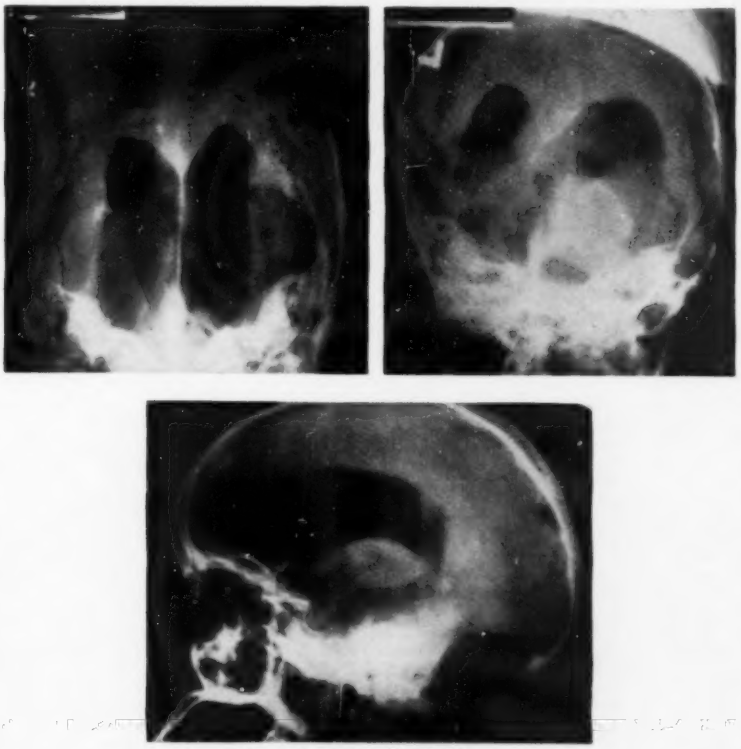

FIG. 426.—*Case* 4. Ventriculogram.

von Recklinghausen's disease with bilateral acoustic neurinomata was made. Since the signs suggested that the left-sided tumour was responsible for the greater part of her symptomatology, it was decided to commence her treatment by its excision.

AT OPERATION.—On May 17 a left suboccipital craniectomy was effected, and, after tapping of the left lateral ventricle, dural flaps reflected. Two pink spherical finely nodular tumours related to the lateral sinus were exposed (*Fig.* 424 A). The first measured 1 cm. in diameter

and was attached to the dura close to the termination of the transverse part of the lateral sinus, being embedded in the posterior margin of the cerebellar hemisphere; the second measured 1·5 cm. in diameter and was attached to the dura over the medial portion of the sigmoid sinus. Both were excised and the bases of attachment cauterized —the sinus being opened in the case of the second tumour and its lumen obliterated with fibrin foam soaked in free from headache, although hearing on the right side slowly failed, with associated right tinnitus. Three and a half years after operation, frontal headache appeared. This was not associated with vomiting, but worsened, and when seen in February, 1958, she was complaining of failing vision and was re-admitted to hospital. It was obvious that she had lost weight. The decompression was flat, but there was low swelling of both disks. There was

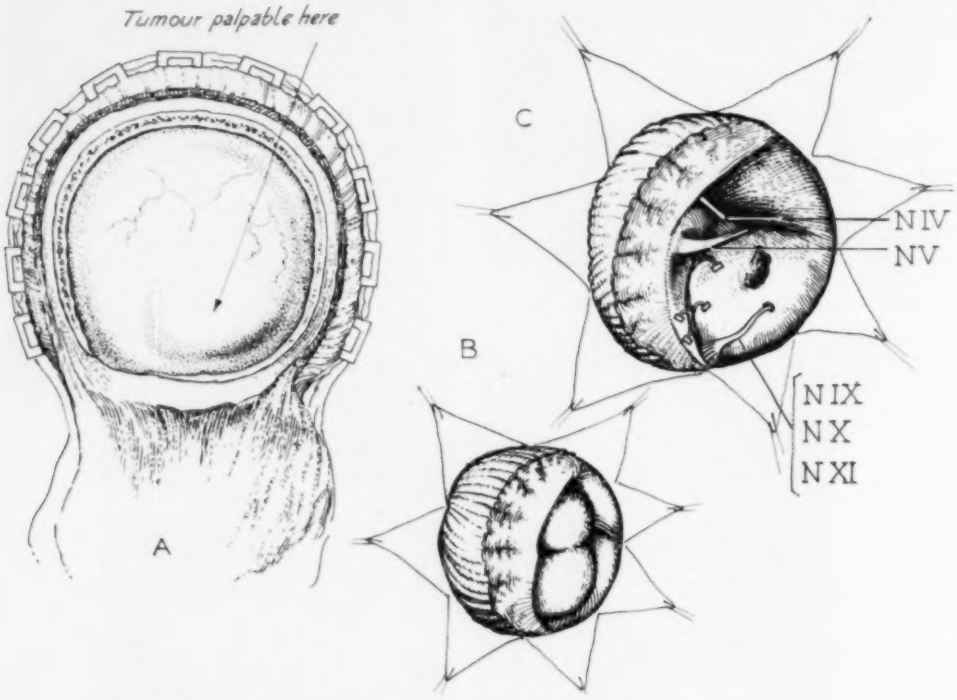

FIG. 427.—*Case* 4. Sketches made during second operation.

thrombin solution. Elevation of the left cerebellar hemisphere revealed a yellowish tumour mass in the cerebellopontine angle without an overlying arachnoid cyst. A little more than the lateral third of the left cerebellar hemisphere was excised and the tumour capsule incised (*Fig.* 424 B) to permit removal of its soft interior by suction. The capsule was separated from the 9th, 10th, and 11th cranial nerves inferiorly, from the tentorium cerebelli and 5th cranial nerve superiorly, and from the cerebellum, pons, and medulla medially. The 7th and 8th cranial nerves were seen entering the mass but were sacrificed. The capsule was then detached from the internal auditory meatus and the tumour in the meatus destroyed by cautery (*Fig.* 424 C). The wound was closed in layers and a left tarsorrhaphy effected. Histological examination revealed that the two small tumours were of identical structure, being fibrillary meningiomata (*Fig.* 425 A) and the large tumour a typical acoustic neurinoma (*Fig.* 425 B).

The patient recovered well from the operation and was walking unaided within two weeks. After four weeks a left hypoglossofacial anastomosis was made and the patient discharged to out-patient physiotherapy. Voluntary movement appeared in the left face three months after the nerve anastomosis and a good cosmetic result was obtained. Her gait improved steadily and she remained a bilateral horizontal nystagmus and the lesions of the left 3rd and 6th cranial nerves had progressed, with an associated proptosis of 5 mm. Both corneal reflexes were greatly reduced and there was hypoalgesia in the left trigeminal field, greater in the first division territory. The right face moved normally and the anastomosis functioned well on the left. There was total deafness and no response to the caloric test on either side. There was no other cranial nerve abnormality apart from hemiatrophy and paralysis of the left side of the tongue. The other abnormal signs were slowness of performance of the finger-nose test and heel-knee tests bilaterally, a gait with a wide base deviating to the right, and a positive Romberg sign. Laboratory investigation revealed nothing abnormal. Radiography revealed increased erosion of the right internal auditory meatus. Ventriculography showed a considerable internal hydrocephalus, with displacement of the 4th ventricle to the left (*Fig.* 426). A pre-operative tarsorrhaphy having been done, the right cerebellopontine angle was explored. When the craniectomy had been completed, tumour was palpable through the dura and cerebellum inferiorly (*Fig.* 427 A). After tapping the right lateral ventricle, dural flaps were reflected and beneath an arachnoid cyst a very large lobulated tumour was exposed in the cerebellopontine angle. The lateral third of the right cerebellar hemisphere was excised (*Fig.* 427 B),

the tumour capsule was incised, and the interior of the growth removed by suction. A prolongation of the upper pole into the tentorial opening was withdrawn, with separation from the trochlear nerve, related vessels, and the trigeminal nerve. Separation from the nerves passing to the jugular foramen was readily effected, but nodules of tumour deeply excavated the pons and medulla and vascular connexions made separation difficult. As a result, division of the attachment of growth to the internal auditory meatus was required at an early stage, with sacrifice of the 7th and 8th cranial nerves. After removal of capsule the internal auditory meatus was cleared of contained growth and cauterized (*Fig.* 427 C). No meningeal tumours were seen and, hæmostasis having been obtained, the wound was closed in layers. Histologically the tumour was a typical neurinoma.

Post-operatively consciousness was quickly regained and no evidence of any severe neurological defect could be made out. However, on the day following operation respiratory stridor with bronchospasm appeared. This at first responded to injections of aminophylline, but on the second post-operative day collapse of the lower lobe of the left lung appeared and tracheostomy was effected, tracheal suction producing immediate re-expansion. The tracheostomy was maintained for 3 weeks, during which time the most careful treatment with appropriate antibiotics and tracheal suction was required to overcome a bronchial and basal pulmonary infection. Nasal feeding was gradually discontinued after this—there being at first great difficulty in swallowing, occasioned apparently by either inco-ordination of the movements of deglutition or the bilaterally reduced sensibility in the anterior tongue, mouth, and lips, since movements of the palate and right half of the tongue were normal.

At the time of her discharge, 3 months after operation, she could walk unaided, though on a wide base. She had begun to gain weight, though swallowing remained difficult. Sensibility was reduced in both trigeminal fields and there was a right facial paralysis. Power and tone in the limbs were excellent, there being no ataxia.

One year after operation she had gained 30 lb. in weight and was swallowing more easily. She was increasing her activities at home and anxious to have treatment for the right facial paralysis. In September, 1959, when a right accessory-facial nerve anastomosis was effected, a considerable further improvement—particularly as regards ataxia—was noted. Six months later the improvement was maintained and the right-sided nerve anastomosis had commenced to function.

In this patient the presence of bilateral acoustic neurinomata was clinically and radiologically obvious and these, together with a probable neurinoma in the left orbit, and the cutaneous lesions, made the diagnosis of multiple neurofibromatosis clear, although the posterior fossa meningiomata were unexpected findings. The therapeutic problem here was one of planning the surgical removal of the acoustic tumours and was solved by excising the one considered to be occasioning symptoms and delaying treatment of the second neurinoma until clear indications for such interference arose. At the present time there are no indications of other intracranial neoplasms, and exploration of the left orbit is not considered necessary.

DISCUSSION

Of special interest in this group of patients are the causation of the multiple neoplasms and the diagnostic and therapeutic problems to which they gave rise. The latter have been discussed. As to causation, the association of intracranial meningiomata and a pituitary adenoma in one patient and a cerebral astrocytoma in another are probably to be regarded as purely coincidental. That such coincidence is quite uncommon is shown by the fact that Cushing's great experience of both meningiomata and hypophysial adenomata includes no case in which both neoplasms occurred together. In only 1 of the 295 intracranial meningiomata was there an associated glioma—a patient with a glioblastoma multiforme of the corpus callosum and a clinically silent calcified meningioma at the junction of the falx and tentorium (Cushing, 1938b). In the patient in whom, following the excision of a mid-dorsal meningioma, a parasagittal tumour of similar nature developed after several years, the association may likewise be purely coincidental. However, meningiomata are relatively uncommon tumours, and the possibility that some unusual tendency towards neoplasia may have been present in the cells of the arachnoid in this case exists—just as it must exist in the cases of multiple intracranial meningiomata not associated with von Recklinghausen's disease. Finally, in the patient with combined multiple meningiomata and multiple neurinomata in the posterior cranial fossa, the causation lies in the inherited abnormality of the neural crest which characterizes neurofibromatosis.

SUMMARY

The case-histories of 4 patients in whom intracranial meningiomata were associated with other tumours involving the central nervous system are described. The aetiology of these multiple tumours is considered and the diagnosis and therapeutic problems which they may occasion are discussed.

In the illustration of this paper I am indebted to the Photographic Department of the Hospital and to Mr. Field Marchant, who elaborated the operative sketches. Dr. R. G. Canti was responsible for the pathological investigation of the material, and provided the photomicrographs. The successful outcome in *Case* 4 was in large measure due to the devoted attention of the nursing staff and that of my then Chief Assistant, Mr. J. Andrew.

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— — (1938b), *Ibid.*, 507.

OBSERVATIONS ON RENAL HOMOTRANSPLANTATION

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THE technique of transplantation of kidneys in man has been evolved with remarkable success by Murray, Merrill, and Harrison (1958). They recently reported 7 cases of identical-twin renal transplants, one patient having survived three and a half years with a kidney whose functions were little different from those of his donor twin (Bricker, Guild, Reardan, and Merrill, 1956).

Tissues exchanged between identical twins are accepted in a similar way to autografts. However, tissues grafted between patients other than twins, with a few exceptions, are rejected by an immunological process, fundamental studies on which were carried out by Medawar (1959).

Although much of the detail of the homograft rejection process is not yet known, in principle it would appear that living transplanted cells liberate a polysaccharide complex associated with the deoxyribonucleic acid of the cell. This acts as an antigen to the host, whose reticulo-endothelial system responds by producing immunologically competent cells, which reach and destroy the foreign tissue. If further tissue from the same donor is introduced, it will be destroyed more rapidly than the first graft, indicating an active acquired immunity.

Assuming the above scheme to be true, attempts to prevent the homograft reaction could be directed at three points, namely:—

1. Modification of the antigenic nature of the graft. This has not yet been achieved without killing the tissue. There is some evidence that early fœtal tissue is not antigenic (May, 1959).

2. Prevention of the antigen reaching the reticulo-endothelial system of the host, or prevention of the active reticulo-endothelial cells reaching the graft.

3. Prevention of the reticulo-endothelial system responding to the antigen.

INVESTIGATIONS

1. Fœtal Homografts.—A 4-month-old calf fœtus was used as donor, the recipient being a 2-week-old unrelated calf. The fœtal kidney was transplanted to the neck; the ureter was brought through the skin. A 3-sq. cm. full-thickness piece of skin was grafted to the flank of the recipient and approximately 1 g. of fœtal thyroid was implanted in the subcutaneous tissue. The kidney produced urine for 12 hours. The skin was rejected after 10 days. The animal was killed 10 days later, the kidney was necrotic, and the thyroid had been rejected.

Although only a single observation, this suggested that fœtal calf tissue at 4 months is antigenic.

2. Attempts to Produce or Utilize 'Immunological Tolerance'.—It has been shown that in certain species, fœtal or neonatal injection of homologous tissue renders the injected animal incapable of subsequently rejecting tissue from the same donor (Medawar, 1956). A similar phenomenon can occur naturally in cattle dizygotic twins with a shared placental circulation (Owen, 1945; Anderson, Billingham, Lampkin, and Medawar, 1951). There is a report of a successful renal homograft between such twins (Simonsen, 1955). This has been repeated in the present series. After 40 minutes of ischæmia during the anastomoses an apparently excellent blood-flow resulted through the organ, yet no urine was produced for 20 days. Then a diuresis occurred and urine continued to flow freely. After 6½ months with the animal on a normal diet and fluids *ad libitum*, the specific gravity of the urine from the transplant was 1004 with a urea content of 73 mg. per cent. There was no proteinuria. The animal was killed and the kidney looked normal macroscopically, but showed focal pyelonephritis on microscopy (*Fig.* 428).

Attempts to produce artificial tolerance by neonatal injection of fresh whole blood in calves were unsuccessful. In one experiment an exchange of 700 ml. of blood was made between 2 animals, both under 24 hours old. In another experiment there was a total exchange of 3·6 l., representing about 30 per cent of the blood-volume estimated by radio-active chromate labelling of the red cells. All 4 animals in these experiments actively rejected skin-grafts from their respective partners and therefore kidney transplants were not performed.

3. Destruction of the Reticulo-endothelial System.—Total body irradiation can render animals tolerant to homologous tissue by destruction of the reticulo-endothelial system. Mannick, Lochte, Ashley, Thomas, and Ferrebee (1959) succeeded in irradiating and re-marrowing a dog and subsequently transplanting a kidney to the irradiated animal from the marrow donor. Over 12 hours 1300 r were given. The animal died from infection 49 days after the kidney transplantation. The kidney was normal microscopically at autopsy.

Attempts by the author to reproduce this experiment have been unsuccessful. A greyhound was given 1300 r over 15½ hours and died 3 days later from acute hæmorrhagic irradiation enteritis. Another greyhound was given 900 r in 2 doses of 450 r separated by 36 hours, and 1·8 billion nucleated marrow cells from a female greyhound were injected intravenously 3 hours after completion of the irradiation. The animal remained well, but there was no evidence of the 'club' leucocyte forms indicative of a successful marrow take (Porter, 1957). Three weeks following the irradiation, the total white-cell count was 400. Five days later it had risen to 1300 and a kidney from the marrow donor was transplanted to the right iliac fossa of the irradiated animal. Ten days later the kidney was explored and found to be swollen, hæmorrhagic, and œdematous (*Fig.* 429). Microscopy showed a typical homograft reaction, as described by Dempster (1953a) and Simonsen, Buemann, Gammeltoft, Jensen, and Jorgensen (1953), with an intense pyroninophylic cellular infiltration of the cortex (*Fig.* 430).

4. Studies with 6-Mercaptopurine.—Following the report of Schwartz and Dameshek (1959) that 6-mercaptopurine can make rabbits specifically tolerant to human serum albumin antigen, a previous investigation was undertaken into the effects of this drug on renal homografts in dogs (Calne, 1960), and the following observations are drawn from this study.

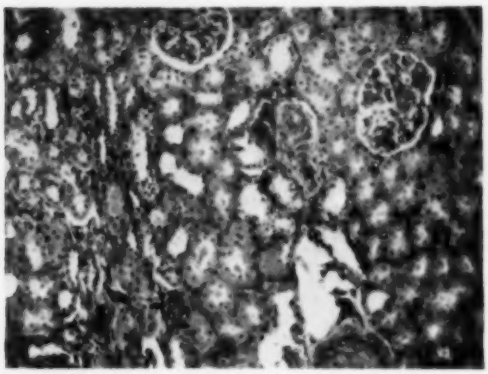

FIG. 428.—Photomicrograph of kidney transplanted from calf dizygotic twin after 6½ months. Shows focal pyelonephritis with periglomerular fibrosis. H. and E. (× 60.)

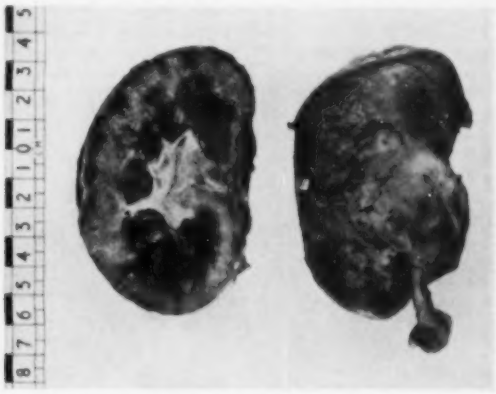

FIG. 429.—Kidney 10 days after transplantation in dog which had received 900 r total body irradiation. The organ is enlarged, hæmorrhagic, and œdematous.

PREVIOUS STUDIES

Methods.—Unrelated dogs were used as donor and recipient. Intravenous pentobarbitone anæsthesia was given, and a kidney removed from the donor and transplanted to the right iliac fossa of the recipient. The renal vessels of the donor's kidney were then anastomosed to the iliac vessels of the recipient, and the ureter was implanted into the bladder. In some animals full-thickness skin-grafts were applied to the scapular region; 6-mercaptopurine was given either by intramuscular injection suspended in methyl cellulose, or orally in tablet form.

There was marked variability in the toxic effects of 6-mercaptopurine. However, 6 mg. per kg. daily was invariably fatal, 2·5 mg. per kg. daily was lethal to some animals, yet well tolerated by others, and 1·5 mg. per kg. daily was relatively non-toxic.

Results.—With one or both of the recipient's own kidneys intact, observations were as follows (*Table I*):—

Two animals, on a high dosage of 6 mg. per kg. daily, died in the second week after transplantation from hæmorrhagic enteritis. The transplant kidneys showed no homograft reaction.

On a lower dosage of between 2 and 3 mg. per kg. daily, 3 animals died from hæmorrhage due to marrow depression 12–17 days after transplantation. None of the kidneys from dogs in this group showed a homograft reaction (*Figs.* 431, 432). However, on the same dosage 4 other animals did have evidence of homograft reaction in their transplants after 8–13 days (*Fig.* 433). Three of these died as a result of the drug; the other died from a peritoneal hæmorrhage, but with a high peripheral white blood-cell count. The cellular infiltration in the transplant of a further animal at this dose level was similar to that in the control kidney of the donor. The animal died after 17 days from bronchopneumonia.

On a dosage under 2 mg. per kg. daily 5 transplants showed homograft reactions. In 1 of these the kidney had been taken from a donor which had been on 6-mercaptopurine for 2 weeks. A biopsy

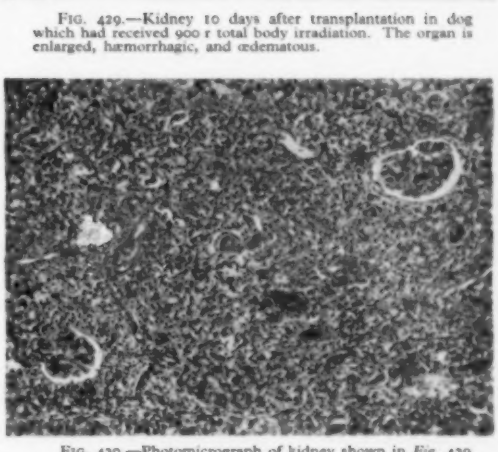

FIG. 430.—Photomicrograph of kidney shown in *Fig.* 429. Shows massive pyroninophylic cellular infiltration of the cortex. H. and E. (× 60.)

of this kidney 14 days after transplantation showed a well-developed homograft reaction. After 47 days the reaction had advanced to necrosis and hæmorrhage.

In order to determine whether 6-mercaptopurine would prolong functional survival in addition to inhibiting the cellular infiltration, in 3 animals bilateral nephrectomy was performed at the time of transplantation (*Table II*).

In the first of these, the donor was a male boxer and the recipient a male retriever. The dose of 6-mercaptopurine was 4·5 mg. per kg. intramuscularly for 2 days, started on the day of transplantation, then 2·5 mg. per kg. daily. The drug was given orally when the animal resumed eating; it was withheld for 6 days because of leucopenia. The dog

Table I.—Effect of 6-Mercaptopurine on Dogs with Renal Homotransplants and One or Both of their own Kidneys Intact

No.	Donor	Recipient	6-MP Dosage in mg. per kg. per Day*	Survival in Days and Cause of Death	Homograft Reaction	Histological Changes other than Homograft Reaction	White Blood-cells and Marrow Depression	Lymphoid Depletion (Spleen and Glands)	Other Factors
1	Alsatian F.	Alsatian M.	6 for 12 d., started 2 d. before transplantation	11. Hæmorrhagic enteritis	Nil	Mild infective pyelonephritis	+ +	+	Intestinal epithelium necrosis
2	Collie F.	Greyhound M.	6 for 8 d., started 1 d. before transplantation	10. Hæmorrhagic enteritis	Nil	Areas of hæmorrhage. Some cellular perivascular cuffing	+ +	+ +	Intestinal epithelium necrosis
3	Boxer M.	Alsatian M.	4 for 2 d., then 2 daily	12. Lung hæmorrhage	Nil		+ +	+	
4	Black mongrel M.	Brown and white mongrel M.	4 for 2 d., then 2 for 7 d.	13. Peritoneal hæmorrhage	Nil	Areas of hæmorrhage. Some calcium in tubules	+ +	+ +	
5	Dark Alsatian M.	Light Alsatian M.	4 for 2 d., 2 for 3 d., 2 d. rest, then 1 till death	17. Lung hæmorrhage	Nil	Hydronephrosis	+ +	+ +	
6	Mongrel F.	Mongrel F.	2 for 6 d., 5 d. rest, 2 for 2 d.	17. Abscess in leg	Nil	Scattered hæmorrhages	+ +	+ +	Own kidney similar hæmorrhages to transplant
7	Light Alsatian F.	Dark Alsatian F.	3 for 7 d., then 1 daily	40. Pneumonia	Nil		Nil	+	Acute pneumonia
8	Dark Alsatian F.	Light Alsatian F.	3 for 7 d.	8. Lung hæmorrhage	+	Occasional hæmorrhage	+ +	+	
9	Boxer M.	Mongrel F.	5·5 alternate d.	8. Peritoneal hæmorrhage	+	Colloid in tubules	Nil	Nil	
10	Alsatian M.	Boxer M.	4 for 2 d., then 2 daily	13. Peritonitis	+	Acute peritonitis and pyelonephritis	+	+	
11	Black greyhound M.	Brown greyhound M.	5 for 3 d., 2·5 for 5 d.	12. Lung hæmorrhage	+		+ +	+ +	Skin-graft normal. Lung hæmorrhage
12	Mastiff F.	Mongrel F.	4 for 2 d., 2 for 8 d.	17. Pneumonia	±	Pyelonephritis	+	+	Bronchopneumonia. Control pyelonephritis
13	Mongrel F.	Mastiff F.	4 for 2 d., 2 for 8 d., then none for 11 d.	24. Killed	+ +		Nil	+	
14	Greyhound F.	Greyhound M.	4 for 2 d., 2 for 3 d., then none for 7 d.	12. ?	+		+ +	+	
15	Greyhound M.	Greyhound F.	4 for 2 d., 2 for 3 d., then none for 7 d.	12. ?	+		+	+ +	Liver fatty
16	Light Alsatian M.	Dark Alsatian M.	4 for 2 d., 2 for 3 d., 2 d. rest, 2 for 8 d., 1 for 14 d.	31. Intussusception	+ +		Nil	Nil	Intestine hæmorrhagic
17	Alsatian M.	Boxer M.	3 on alternate d. for 14 d., 4 for 2 d., 3 daily	47. Killed	+ +		Nil	+	Donor had been on 6-mercaptopurine for 2 wk. at a dose varying from 4–2 mg. per kg. daily

* Started on day of transplantation unless otherwise stated.

became fit and passed urine satisfactorily. After 3 weeks the blood-urea fell to between 35 and 40 mg. per cent (*Fig.* 434) and remained at this level. It unfortunately developed a respiratory infection, which only partially responded to antibiotics. It became anorexic and jaundiced and died 47 days after transplantation. At post-mortem the kidney and ureter were macroscopically normal (*Fig.* 435) and microscopy of the transplant showed no homograft reaction (*Fig.* 436). There were scattered areas of non-pyroninophylic cellular infiltration considered to be infective in origin. The lungs showed acute pneumonia, the liver contained bile thrombi and scattered areas of necrosis. The spleen was depleted in lymphoid tissue, but the bone-marrow was active (*Fig.* 437). The total white-cell count 11 days before death was 14,000 with a differential of 89 per cent neutrophils and 9 per cent lymphocytes. The blood-film showed a regenerative picture.

In the second experiment the donor was a male collie and the recipient a male labrador. The dose of 6-mercaptopurine was 5 mg. per kg. intramuscularly for 2 days, started on the day of transplantation, then 2 mg. per kg. orally. The animal developed pneumonia and had two fits on the nineteenth day, when his blood-urea had fallen to 43 mg. per cent. He died on the twenty-first post-operative day. The total white blood-cell count 5 days before death was 19,000 with a differential of 91 per cent neutrophils and 7 per cent lymphocytes, and the blood-film showed a regenerative picture. The dog had had no 6-mercaptopurine for the previous 14 days. Microscopy of the transplant showed scattered areas of hæmorrhage and some glomerular crescents, with an otherwise fairly normal parenchyma and no cellular infiltration (*Fig.* 438).

In the third experiment a skin-graft was performed at the time of renal transplantation. In spite

FIG. 431.—Kidney 40 days after transplantation in dog on 6-mercaptopurine. Normal appearance.

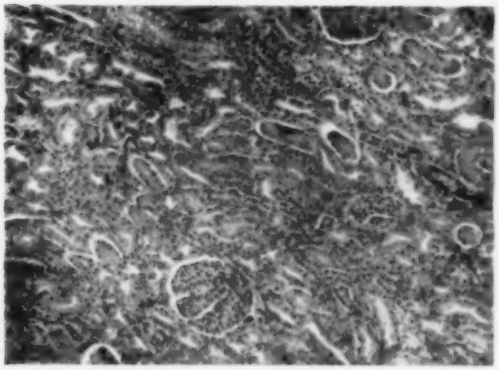

FIG. 432.—Photomicrograph of kidney shown in *Fig.* 431. Normal appearance. H. and E. (× 60.)

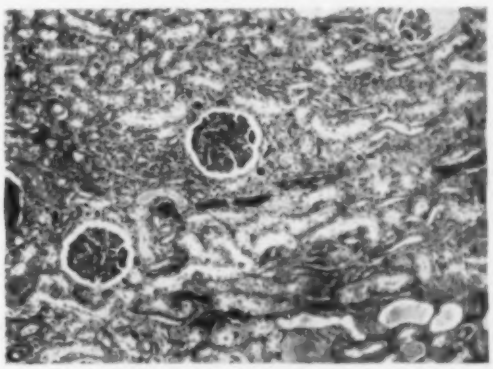

FIG. 433.—Photomicrograph of kidney 12 days after transplantation in dog on 6-mercaptopurine. Shows focal areas of pyroninophylic cortical cellular infiltration. H. and E. (× 60.)

Table II.—EFFECT OF 6-MERCAPTOPURINE ON DOGS WITH RENAL HOMOTRANSPLANTATION FOLLOWING BILATERAL NEPHRECTOMY

No.	DONOR	RECIPIENT	6-MP DOSAGE IN mg. PER kg. PER DAY*	SURVIVAL IN DAYS AND CAUSE OF DEATH	HOMOGRAFT REACTION	HISTOLOGICAL CHANGES OTHER THAN HOMOGRAFT REACTION	WHITE BLOOD-CELLS AND MARROW DEPRESSION	LYMPHOID DEPLETION (SPLEEN AND GLANDS)	OTHER FACTORS
18	Boxer M.	Retriever M.	4·5 for 2 d., then 2·5 daily; 6 d. rest	47. Pneumonia	Nil	Very occasional non-pyroninophylic cellular infiltration	Nil	++	Intrahepatic bile stasis
19	Collie M.	Labrador M.	5 for 2 d., then 2 for 5 d.	21. Pneumonia	Nil	Scattered hæmorrhages	Nil	++	
20	Labrador M.	Alsatian F.	3 daily	14. Uræmia	++		Nil	++	Skin-grafted. Intestinal hæmorrhage

* Started on day of transplantation unless otherwise stated.

of a dose of 6-mercaptopurine of 3 mg. per kg. daily the transplant developed a homograft reaction, and the animal died after 14 days from uræmia. However, the skin-graft was still living and showed only minimal cellular infiltration at the edges.

The results of the action of 6-mercaptopurine on the survival of skin-grafts in dogs have been variable,

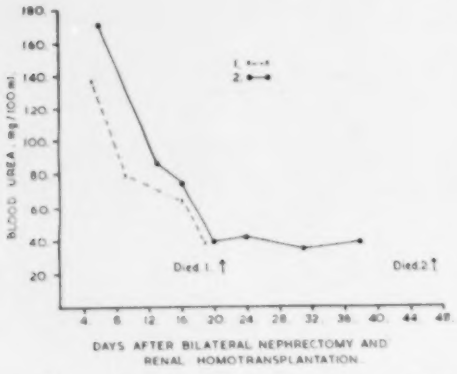

FIG. 434.—Blood-urea levels in animals surviving 21 and 47 days after bilateral nephrectomy and renal homotransplantation.

although significant prolongation has not been achieved. Of 4 dogs on a dosage of 2 mg. per kg. daily by mouth, 1 died from hæmorrhage into the lung on the twelfth day, having itself removed the skin-grafts, and there was severe lymphoid and marrow depletion; 3 rejected skin-grafts during the third week; 2 of them were killed after 35 days.

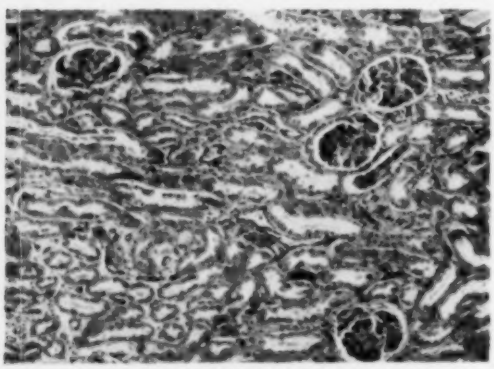

FIG. 436.—Photomicrograph of kidney shown in *Fig.* 435. No evidence of homograft reaction. H. and E. (× 60.)

There was no lymphoid or marrow depletion. One dog remained fit on the same dose of 6-mercaptopurine; it gained weight and was in good health 3 months later. Another animal on 3·5 mg. per kg. daily rejected the skin-graft after 19 days, also with no lymphoid depletion.

Three animals on 2·5 mg. per kg. daily, skin-grafted at the same time as the renal transplantation, rejected the skin-graft during the second week. In one the kidney showed an early homograft reaction, in the others the renal vessels had thrombosed due to technical failure.

The following experiments have been performed to determine the effect of 6-mercaptopurine on second-set homografts: (*Table III*).

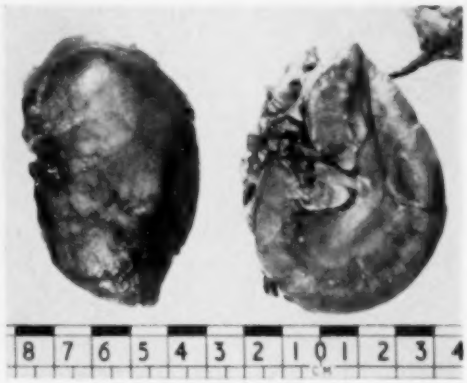

FIG. 435.—Kidney and ureter 47 days after bilateral nephrectomy and renal homotransplantation on 6-mercaptopurine. Normal appearance.

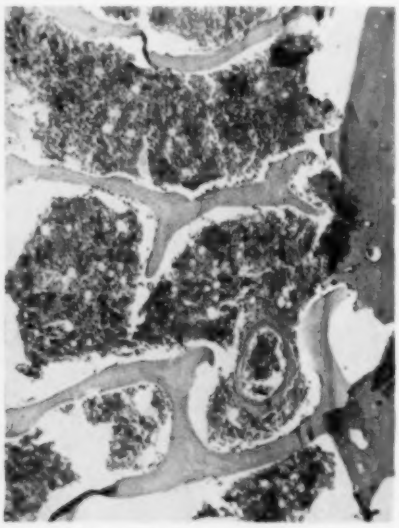

FIG. 437.—Photomicrograph of rib marrow of recipient of kidney shown in *Figs.* 435, 436. Shows active functional marrow. H. and E. (× 45.)

Two animals were skin-grafted reciprocally without 6-mercaptopurine; the grafts were rejected after 9 days. Twelve days later kidneys and further skin-grafts were exchanged between these animals, which were then given 2·5 mg. per kg. of 6-mercaptopurine daily. One dog died after a further 10 days with peritonitis; there was a well-developed renal homograft reaction, though the skin-graft was intact with

minimal cellular infiltration microscopically. A week after transplantation the other animal at laparotomy was seen to have a normal-looking transplant kidney, although his second-set skin-graft was undergoing rejection. His own remaining kidney was removed and a 20-cm. ileo-colic intussusception was discovered and reduced. He passed urine satisfactorily, but became jaundiced and developed a severe respiratory infection. He died following a series of fits 15 days after transplantation. His blood-urea was 40 mg. per cent on the day before he died; the transplant kidney looked normal and showed minimal cellular infiltration on microscopy (*Fig.* 439). The liver was necrotic.

Another animal which had actively rejected both skin and a kidney (*Fig.* 440) after 14 days was subjected to unilateral nephrectomy, a further renal transplant, and skin-graft from the same donor. She

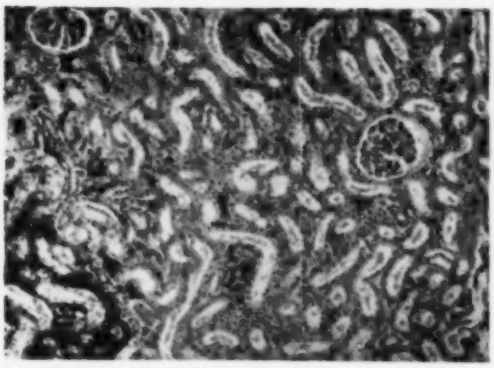

FIG. 438.—Photomicrograph of kidney 21 days after bilateral nephrectomy and renal homotransplantation on 6-mercaptopurine. No evidence of homograft reaction. H. and E. (× 60.)

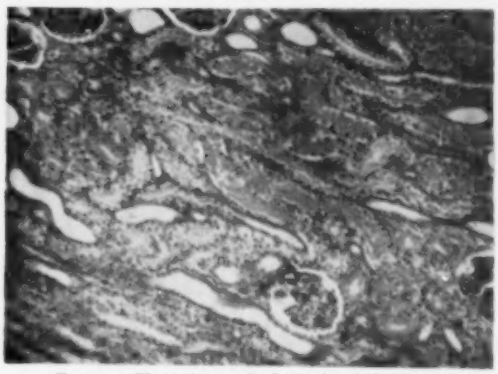

FIG. 439.—Photomicrograph of second-set kidney in animal sensitized by skin-grafts. Fifteen days after transplantation. Minimal cortical cellular infiltration. H. and E. (× 60.)

Table III.—EFFECT OF 6-MERCAPTOPURINE ON SECOND-SET RENAL HOMOTRANSPLANTS

No.	Donor	Recipient	First Set	Result	Second Set	Result	White Blood-cells and Marrow Depression	Lymphoid Depletion (Spleen and Glands)	Other Factors
21	Brown mongrel M.	Black mongrel M.	4·2 sq. cm. full-thickness skin homografts	Rejection after 9 d.	Skin 2 × 1 cm. and kidney 21 d. after commencement of 1st set	Died from peritonitis after 10 d. Renal transplant homograft reaction, skin minimal infiltration at edges	Nil	+	Focal liver necrosis. Broncho-pneumonia
22	Black mongrel M.	Brown mongrel M.	4·2 sq. cm. full-thickness skin homografts	Rejection after 9 d.	Skin 2 × 1 cm. and kidney 21 d. after commencement of 1st set	Died, bronchopneumonia after 15 d. and 8 d. after removal of remaining kidney. Minimal homograft reaction in kidney, skin rejected	Nil	+	Intussusception reduced. Severe liver necrosis
23	Alsatian M.	Mongrel F.	2 sq. cm. full-thickness skin homograft. Renal transplant	Rejection after 14 d.	Immediate 2nd-set skin and kidney. Unilateral nephrectomy	Died, peritoneal hæmorrhage after 20 d. and 13 d. after removal of own remaining kidney. Skin rejected	Nil	+ +	Broncho-pneumonia
24	Mongrel F.	Mongrel M.	2 sq. cm. full-thickness skin homograft. Renal transplant	Florid rejection after 7 d.	Immediate 2nd-set kidney	Initial good blood flow, kidney went blue after 5 min., black after 10 min. Acute intrarenal vascular disruption			
25	Mongrel M.	Mongrel F.	2 sq. cm. full-thickness skin homograft. Renal transplant	Florid rejection after 7 d.	Immediate 2nd-set kidney	Initial good blood-flow, kidney went blue after 5 min., black after 10 min. Acute intrarenal vascular disruption			

was then given 2·5 mg. per kg. of 6-mercaptopurine daily. Fourteen days later the skin had been rejected, but at laparotomy the transplant looked normal, although a biopsy showed an early homograft reaction. Her own remaining kidney was removed and with only the second-set transplant she passed urine satisfactorily for 4 days. She died 20 days after the second transplant from an intraperitoneal hæmorrhage. The transplant looked normal macroscopically, but showed a mild homograft reaction on microscopy (*Fig.* 441).

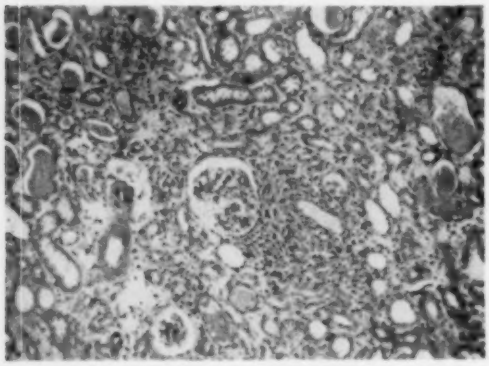

FIG. 440.—Photomicrograph of first-set kidney after 14 days. Shows moderately advanced homograft reaction. H. and E. (× 60.)

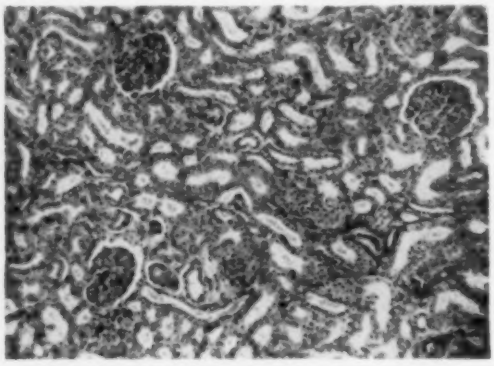

FIG. 441.—Photomicrograph of second-set kidney (first-set, *Fig.* 440) after 20 days on 6-mercaptopurine. Shows only slight cortical cellular infiltration. H. and E. (× 60.)

Two further attempts to repeat this experiment produced quite different results. One week after reciprocal renal transplantation and skin-grafting, at laparotomy a well-advanced homograft reaction was found in the transplants of both animals. Renal transplantation from the same donor resulted in each case in an initially satisfactory blood-flow, but within 5 min. the renal cortex became purple and then black. The renal artery and vein were still fully patent and a small blood-flow still passed through the kidney. This was demonstrated by clamping the renal vein and incising it on the renal side of the clamp. After 45 min. the kidneys were removed. Microscopy showed the acute vascular disintegration of a second-set kidney (*Fig.* 442) as described by Dempster (1953a).

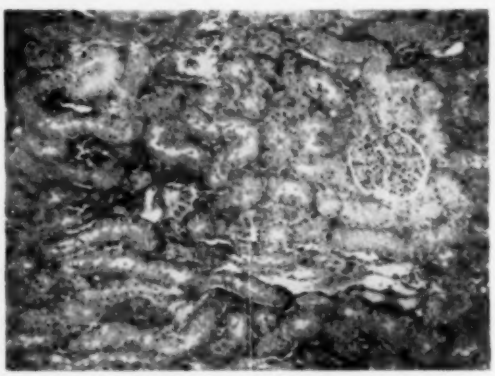

FIG. 442.—Photomicrograph of second-set kidney. Showing acute vascular disruption after 45 minutes. H. and E. (× 60.)

OBSERVATIONS WITH HETEROGRAFTS

A goat's kidney was transplanted into the iliac fossa of a dog. An acute reaction occurred, apparently identical to that in the second-set experiment described above. There was an initial good blood-flow through the kidney, then after 5 min. the renal cortex became pale, and then blue, although there was an excellent pulsation in the renal artery. Tension in the kidney diminished and a clamp on the renal vein did not produce renal engorgement. After 30 min. the cut end of the ureter stopped bleeding; after 90 min. the renal artery thrombosed and the kidney was removed. Microscopy showed acute vascular disintegration with hæmorrhages in the juxta-medullary region (*Fig.* 443). The dog was then grafted with a 4-sq. cm. full-thickness piece of goat's skin and it was given 6-mercaptopurine, 3 mg. per kg. daily. After 11 days the skin was soft and intact, but in the course of the following week the graft gradually hardened. The dog died with an upper respiratory infection 21 days after grafting. The skin was dead.

Two further goat-to-dog skin heterografts were performed. One dog was given 3 mg. per kg. of 6-mercaptopurine daily and the other no drug. The treated animal's graft was rejected after 12 days and the control after 6 days.

DISCUSSION

In dogs, unmodified first-set renal homografts usually cease to function after 4–8 days. The longest periods of function in 4 recent series were 18 days (Dempster, 1953b), 12 days (Simonsen, 1955), 14 days (Egdahl and Hume, 1955), and 20 days (de Klerk, Scott, and Scott, 1954). The above observations suggest that 6-mercaptopurine can inhibit the rejection of renal homografts in dogs.

Although steering the dosage between the Scylla of marrow aplasia and the Charybdis of a homograft reaction has proved very difficult, it has been possible to demonstrate a functioning renal homograft in an

animal with a satisfactory white-cell count and marrow histology after 47 days. However, some animals on a toxic dose of the drug have nevertheless rejected renal homografts.

The mode of action of 6-mercaptopurine is by no means clear. The difference in its action on skin

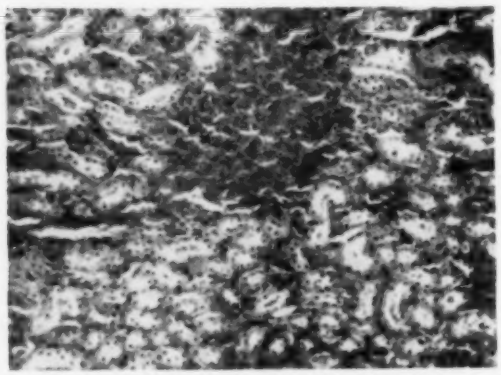

FIG. 443.—Photomicrograph of goat with dog renal heterotransplant after 90 minutes. Showing acute vascular disruption with juxta-medullary hæmorrhages. H. and E. (× 60.)

and renal homografts cannot at present be explained. Possible significant factors could be:—

1. A considerable proportion of 6-mercaptopurine passes through the kidneys and is excreted in the urine.

2. A difference in antigen dosage; 6-mercaptopurine seems to be most active against rapidly dividing cells, and a more extensive reticulo-endothelial mobilization would be expected with an immediately vascularized organ transplant than with a skin-graft.

3. A different mechanism of rejection in the two tissues.

The drug can be hepato-toxic and it certainly increases the liability to infection in dogs after surgery. However, an animal on 2 mg. per kg. daily without surgery has maintained good health for 3 months.

The experiments with second-set transplants demonstrate the wide variations in the rejection reaction in dogs. In animals Nos. 24 and 25 (*Table III*) the unmodified homograft reaction had advanced to a far greater degree in 7 days than in animal No. 23 after 14 days. The subsequent behaviour of the second-set transplants would appear to indicate that in dogs Nos. 24 and 25 there was a high degree of incompatibility between the kidney and the recipient's blood, resulting in an immediate and explosive reaction very similar to that observed with the goat–dog heterotransplant. However, not only was this not so in dog No. 23, but with this sensitized animal treated with 6-mercaptopurine from the time of the second-set transplant, the homograft reaction proceeded more slowly than the first-set reaction.

Although 6-mercaptopurine has the obvious disadvantages of being active only at a potentially toxic dose, and even then not being effective in every case, it may nevertheless offer an approach to renal homotransplantation in man, especially in chronic uræmic patients in whom homograft rejection is already depressed (Hume, Merrill, Miller, and Thorn, 1955).

SUMMARY

A variety of observations has been made on renal transplants in animals. Inhibition of the usual rapid immunological rejection of renal homografts in dogs has been demonstrated by the purine analogue 6-mercaptopurine in a dose near to the LD_{50}.

Acknowledgements.—I would like to acknowledge with gratitude the help that I have had from many different sources, especially from Professor David Slome under whose direction this work has been carried out. I am indebted to him and to Mr. J. P. Hopewell and Dr. K. A. Porter for advice and guidance. I wish to express my gratitude to the Council of the Royal College of Surgeons of England for permission to work at the Buckston Browne Research Farm, and to the Department of Physiology of the Royal College of Surgeons for the grant which made this research possible. My thanks are due also to Professor W. D. Smithers, Professor C. Formston, and Dr. W. S. Gordon, in whose departments some of the experiments were undertaken. I thank Mr. W. D. Tavernor and Mr. C. D. Bracewell for their veterinary assistance and Mr. F. Watson, Mr. R. A. F. Hollis, and Mr. G. F. Eely for technical help. The departments of Pharmacy, Pathology, and Photography of the Royal Free Hospital gave their specialized assistance, and I wish to thank Messrs. Burroughs Wellcome & Co. for generous supplies of 6-mercaptopurine.

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MECKEL'S DIVERTICULUM

By J. L. A. DOWSE

THE ROYAL INFIRMARY, UNITED CARDIFF HOSPITALS

ILEAL diverticula have been recognized for many hundreds of years, and McParland and Kiesewetter (1958) refer to the earliest report by Hildanus in 1598. Ruysch (1707) and Littré (1719) also published cases of ileal diverticula, but it was Meckel who described two distinct types of diverticula of the ileum in his original paper in 1809. The acquired type arises from the mesenteric border, and is often formed of mucosa only, whereas the other arises from the circumference of the ileum apart from the mesenteric attachment, and these latter have a complete muscular layer. Meckel recognized these as congenital diverticula, remnants of the vitello-intestinal tract, and to which the synonym 'Meckel's' diverticulum now applies. Since Meckel wrote his paper, other authors (Greenblatt, Pund, and Chaney, 1936; Schwartz, 1956) have included diverticula within the mesenteric folds as Meckel's diverticula. These cannot be remnants of the omphalo-mesenteric duct which must arise from the free unattached circumference of the embryo midgut.

Table I.—AGE AND SEX INCIDENCE IN 100 CASES OF MECKEL'S DIVERTICULUM

AGE IN YEARS	NO. OF CASES		
	Total	Males	Females
0–10	32	25	7
11–20	18	13	5
21–30	16	12	4
31–40	9	5	4
41–50	11	5	6
51–60	7	4	3
61–70	5	4	1
71–80	2	2	—
Total	100	70	30

With this in mind, variations in recorded incidence of Meckel's diverticulum can be explained. Treves (1918) records an incidence of 1–2 per cent. Mottram and Garland (1945) report its presence in 2 per cent, and Mitchell, of Chicago (quoted by Cobb, 1936), records its presence in 2·38 per cent of necropsies; Rich, however, of the Johns Hopkins Hospital (quoted by Owen and Finney, 1949), found an incidence of only 0·73 per cent in 17,000 autopsies. It may be that the incidence is highest where the diverticula are especially sought and recorded, or perhaps, as is most probable, when diverticula other than remains of the omphalo-mesenteric duct are included as Meckel's diverticulum.

It has been possible to collect 100 cases of Meckel's diverticulum from the records of the United Cardiff Hospitals and from the East Glamorgan Hospital. In this series 70 per cent were male and 30 per cent female; 32 per cent were children less than 10 years old. Of the 100 cases, in 67 per cent a Meckel's diverticulum was the cause of the disease process leading to operation. Gross (1953), reporting on the condition in children, records an incidence of 50 per cent in the 0–2-year-old age-group, and a sex ratio of 3 males to 1 female. The age and sex incidence of this series is shown in *Table I*.

PRESENTATION

The mode of presentation in this series of 100 cases can be seen in *Table II*, and from this it can be seen that Meckel's diverticulum produces disease in four main ways:—

1. Intestinal obstruction.
2. Peptic ulceration.
3. Inflammation.
4. Tumour.

About a third of the cases were found incidentally at laparotomy, and a small number (2 per cent) presented with an umbilical fistula.

1. Intestinal Obstruction.—Walsh (1949), reporting on cases of intestinal obstruction, found that a Meckel's diverticulum was the cause in 6 per cent. In 27 cases of this series obstruction of part of the small bowel was the presenting condition. The diverticulum alone may become gangrenous if its blood-supply is cut off, and this happens if the diverticulum becomes twisted on its base or when included within a hernial sac. Littré (1719) described the syndrome produced by the strangulation of a Meckel's diverticulum in an inguinal hernial sac, laying down the following clinical criteria:—

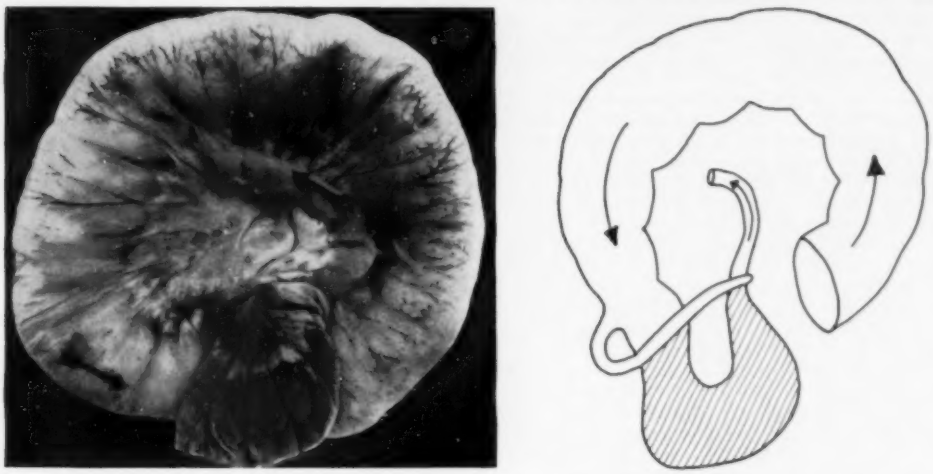
1. As the intestinal canal is not occluded the passage of flatus and fæces is uninterrupted.
2. The abdomen remains flat and does not become distended.
3. Patients rarely vomit and the vomitus is never fæculent.

Table II.—PRESENTING DISEASE STATE WITH AGE VARIATION

PRESENTATION		NUMBERS			AGE	RANGE
		Total	M.	F.		
Intestinal bleeding		10	7	3	3 mth.	22 yr.
Intestinal obstruction		27	21	6	5 d.	80 yr.
Adhesions		17	13	4	5 d.	80 yr.
Intussusception		5	5	—	5 mth.	16 yr.
Vitello-intestinal band duct		3	1	2	22 yr.	43 yr.
Tumour		2	2	—	54 yr.	76 yr.
Volvulus		2	2	—	10 yr.	27 yr.
Generalized peritonitis		10	7	3	9 yr.	76 yr.
Perforated	peptic ulcer	3	2	1	48 yr.	57 yr.
	tumour	1	1	—	76 yr.	
	trauma (foreign body)	2	1	1	9 yr.	60 yr.
	inflammation	4	3	1	14 yr.	50 yr.
Acute inflammation		16	11	5	6 yr.	46 yr.
Patent omphalo-mesenteric duct		2	2	—	3 wk.	7 mth.
Chronic abdominal pain		13	10	3	31 yr.	66 yr.
Exomphalos		1	1	—	5 hr.	
Incidental finding		33				

4. The swelling in the groin is formed slowly and enlarges progressively; at the same time toxic signs become more manifest.

A strangulated Meckel's diverticulum within any hernial sac is now accepted as a 'Littré's hernia'. In one case in this series a diverticulum was found during inguinal herniorrhaphy, but as its vascular supply was unaffected, it cannot be included as a Littré's hernia.



A B

FIG. 444.—A, Post-mortem specimen showing small diverticulum forming a bridge, beneath which a small loop of ileum is strangulated. The arrows lie on dilated proximal and collapsed distal ileum. B, Schematic plan of A.

In 17 cases the diverticulum was attached at its distal end by adhesions to the umbilicus (vitello-intestinal band), to the mesentery, or some other part of the peritoneum, forming a bridge beneath which part of the intestinal canal had been ensnared. The youngest patient of this type was only 5 days old. *Fig.* 444 is a photograph of a specimen in the pathology museum at the Royal Infirmary, Cardiff. This was obtained at post mortem from a child aged 10 years who was admitted *in extremis* 4 days after the onset of intestinal obstruction. Death occurred before resuscitation was of value. The photograph shows a small strangulated loop beneath a narrow diverticulum, adherent at its tip to the mesentery with the distended proximal and collapsed distal ileum. *Fig.* 445 is the resected specimen from a case of intestinal obstruction in a young man. The apex of the diverticulum was attached to the mesentery, beneath which the ileum had become strangulated.

When adhesion of the apex of a Meckel's diverticulum occurs to the parietal peritoneum, volvulus of the small intestine may occur around this axis. This condition was found in 2 cases in this series; both were males, aged 10 and 27 years, and were admitted with symptoms of intestinal obstruction. At laparotomy congenital vitello-intestinal bands were found and in each case volvulus of the loop of ileum from which the diverticulum arose had occurred.

Ileo-ileal intussusception may begin with invagination of a Meckel's diverticulum, and this was found in 4 cases in this series. The youngest patient was aged 5 months and the eldest 16 years. This latter case was reported previously by Foster (1947). The invaginated diverticulum which formed the apex of the intussusceptum was enlarged by a submucous

FIG. 445.—Resected gangrenous ileum. The roughened tip of the Meckel's diverticulum formed a bridge, beneath which the bowel had become ensnared.

lipoma. In yet another case the apex of the diverticulum was lined with gastric mucous membrane which had produced peptic ulceration. Presumably abnormal peristaltic movements had produced the inversion of the diverticulum and its intussusception. No obvious reason was found in the other 2 cases to account for the inversion of the diverticulum.

Clark (1944) reported a double intussusception complicated by a complete volvulus through 360°. Harkins (1933) reviewed 160 cases of intussusception due to the invagination of a Meckel's diverticulum, and Ponka (1956), reporting 54 cases, writes that this is common in the adult, and a long history of recurring bouts of periumbilical pain, often over many months or years, precedes the acute attack. Doolin (1929)

records the finding of a Meckel's diverticulum in an inguinal hernial sac, returning it into the abdomen, only to carry out a laparotomy six days later to find an ileoileal intussusception, the apex of which was the diverticulum.

A fifth case of intussusception in this series should be recorded, as in this case a diverticulum was found incidentally at laparotomy and removed by ligating its base and burying the cut surface as one does an appendix stump. The invaginated stump caused an intussusception to occur in the post-operative period. This method of removal is not recommended, as not only may the stump become intussuscepted as in this case, but it is well recognized that heterotopic gastric mucous membrane may be present at the neck of the diverticulum and its removal by this method may leave ectopic tissue behind. Furthermore, the ligature at the base of the diverticulum may slip, with release of intestinal content. Resection of the diverticulum with a wide cuff of ileum is advised, with reconstruction of the ileum.

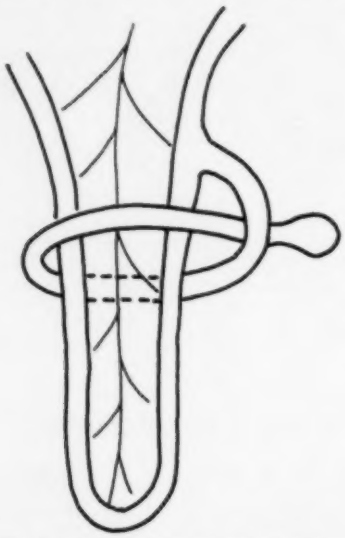


FIG. 446.—Knot formed by a Meckel's diverticulum. (Not a copy of Regnault's original.) (*Ascribed to Regnault.*)

One case of intestinal obstruction due to an argentaffin tumour of a Meckel's diverticulum occurred, but this will be referred to in the section on tumours.

A true knot of a diverticulum is formed rarely, but when it does so, the diverticulum is always long, mobile, and unattached, and has a distal ampullary dilatation, designated by French authors '*la clef de l'étranglement*'. Many variations in the way the small bowel can become obstructed by the knot have been described, and were reviewed by Walsh (1949). *Fig.* 446 is a reproduction of a pen and ink drawing made by a surgeon at operation of a case in this series; this form of knot is ascribed to Regnault.

2. Peptic Ulceration.—Meckel's diverticulum is frequently the seat of heterotopic mucous membrane, and gastric mucosa is found most commonly. So much so that French writers refer to the diverticulum as '*le petit estomac*'. As a result of the presence of heterotopic gastric mucous membrane secreting both hydrochloric acid and pepsin, peptic ulceration may occur in a Meckel's diverticulum or adjacent ileum. These ulcers may erode a vessel, producing intestinal hæmorrhage, or the wall of the diverticulum, causing perforation and peritonitis.

Ileal mucosa is extremely susceptible to peptic digestion, as the small intestine becomes progressively more sensitive to gastric juice as the distance from the stomach increases. Experimental work by Matthews and Dragstedt (1932) produced ulceration in a diverticulum by transplanting a Pavlov pouch into it, and Heubschmann (1913) compared ulceration in this site with anastomotic ulceration following gastro-intestinal anastomoses. Secretion of gastric juice from the stomach is controlled by both neurogenic and hormonal influences. These factors also control the activity of heterotopic gastric mucous membrane within a Meckel's diverticulum, and secretion will occur from both stomach and diverticulum synchronously. The ileum at this time is empty of food content, and so the acid secretions remain un-neutralized, causing erosion of the unprotected ileal mucous membrane. Cobb (1936), recording 100 cases of peptic ulceration in Meckel's diverticulum, described the distribution of ulceration in 45 cases. In 66 per cent the ulcers occurred in a narrow strip encircling the base of the diverticulum at its ileal attachment. As Fojcik (1957) remarks, there is usually a well-defined line of demarcation between ileal and gastric mucosa. This is of course true, but on re-examining histology slides of Meckel's diverticulum reported previously as lined with ileal mucosa only, small islets, even isolated tubules, of gastric glands have been found.

Essentially, symptoms from peptic ulceration in a Meckel's diverticulum begin in infancy, presenting most commonly with brisk intestinal hæmorrhage; 74 per cent occur before 15 years of age. There is also a striking difference of incidence in the sexes, ulceration occurring in the male four times as commonly as in the female. Peptic ulceration in a diverticulum is associated with an ulcer-type pain, usually just below and to the right of the umbilicus, which is not relieved by alkalis. Meteorism is frequently present and relief or aggravation of pain frequently follows defæcation or the passing of flatus (Raffensperger and Mankunas, 1950).

In 8 cases of this series rectal hæmorrhage was the presenting symptom. There is a typical periodicity of bleeding from a Meckel's diverticulum, and the blood lost is characteristically maroon-coloured, with an absence of mucus, as in intussusception, and pus cells, as in colitis (Haber, 1947). Though this condition occurs most commonly in children, Fojcik (1957) reported a case of which symptoms began in a woman of 73 years. Peptic ulceration of a Meckel's diverticulum should be suspected when gastro-intestinal hæmorrhage is otherwise unexplained.

In this series, cases presenting with hæmorrhage varied from 3 months to 22 years of age. The latter case occurred in a male medical student who had a severe hæmorrhage rectally twenty-fours before the

final M.B. examination. It was thought he had had an acute duodenal ulcer, brought on by the impending examination, though he denied strongly that he was the 'ulcer type'. Investigations were all negative for duodenal ulcer and after five weeks of enforced gastric dieting he was discharged. He continued to have almost continuous lower abdominal pain just to the right of the umbilicus and was submitted to laparotomy three years later. At operation a Meckel's diverticulum with an accessory distal diverticulum was found. It was lined with gastric mucosa which had produced ulceration of the diverticulum, and following its removal symptoms disappeared and the patient has remained well.

3. Inflammation.—Inflammation of a Meckel's diverticulum may be acute or chronic and of specific or non-specific nature, traumatic from the presence of a foreign body, or even parasitic in origin (Mahanti, 1958). Of the specific infections, ileo-cæcal tuberculosis and typhoid may involve a diverticulum (included by Nygaard and Walters, 1937). Crohn's disease has been reported on a number of occasions, and Ekman (1958) records the coexistence of these two conditions; in 27 patients found at laparotomy to have regional ileitis, a Meckel's diverticulum was present in 5 cases.

Table III.—THE AGENTS PRODUCING PERFORATION IN 30 REPORTED CASES

PERFORATING AGENT	NO. OF CASES
Fish bones	19
Wooden splinters	3
Rolled tomato skin	3
Sewing needles	2
Gramophone needle	1
Cabbage stalk	1
Grape seeds	1
Total	30

The mouth of a Meckel's diverticulum is usually wide, approximating the diameter of the ileum, and as the contents of the ileum are still fluid, obstruction and stagnation of the diverticular contents or retention of foreign bodies are unlikely. However, a number of cases of foreign bodies present within diverticula have been recorded. Boldero (1958) found 16 cases of intradiverticular radio-opaque calculi in the literature, and reported yet another case in a male aged 61 years. At laparotomy this patient was found to have a Meckel's diverticulum and a gall-bladder packed with calculi. The nucleus of the diverticular stones was thought to be biliary in origin as it contained bilirubin and cholesterol; the laminated shell of organic material, calcium carbonate, and phosphate was formed within the bowel through changes of content associated with variations of *p*H (Fowweather, 1955). Duncan (1956) reported a case of enterolith formation in a diverticulum bound down to the mesentery by a congenital band. It was thought that in this case the adhesion produced stagnation of ileal contents within the diverticulum, with stone formation. It has been suggested that extrinsic foreign bodies, e.g., plum stones, may rarely become the nuclei of diverticular calculi.

"Perforation of a Meckel's diverticulum due to foreign body is exceedingly rare", wrote Gillette and Zoltowski (1957). They reported a total of 26 cases of foreign-body perforation, and put on record a further case of perforation due to a fish bone. This patient admitted to eating fish at least six months prior to his illness! The agents causing perforation can be seen in *Table III*.

In this series of 100 cases 2 further cases of foreign-body perforation are recorded. Including a case reported by Reinalda (1958) and another by Rumore (1958), this brings the total of recorded cases to 30. One case in this series was in a 60-year-old female who was admitted as an emergency with generalized peritonitis. At laparotomy a fish bone, 1 in. long, was found protruding through a puncture wound in a Meckel's diverticulum. The second case was a male child of 9 years, who at operation was found to have a perforation of a diverticulum produced by tightly rolled tomato skin. This is the third reported case of perforation in this way. It is not easy to explain how tomato skin, cabbage stalk (MacFarlane, 1948), or any vegetable matter is able to penetrate the wall of a 'normal' diverticulum, and it may be that the presence of the foreign body within a diverticulum sets up an inflammatory reaction, with œdema and congestion of the diverticular wall; abnormal peristaltic movements may then force relatively blunt structures through a wall softened by inflammation.

The clinical picture of perforation of a diverticulum is indistinguishable from that of peritonitis due to a perforated acute appendicitis, though the latter presents usually more signs of toxæmia. It is wise to emphasize at this point that if the appendix is found at laparotomy to be only slightly inflamed, a search of the small intestine for at least 6 ft. is recommended to ensure that no Meckel's diverticulum is present and the cause of the disease.

One case in this series is of particular interest, illustrating this point. At a laparotomy through McBurney's incision for symptoms suggestive of acute appendicitis a slightly inflamed appendix was found. The ileum was searched for about 30 in. for a Meckel's diverticulum and none found. The patient did not improve after the operation and developed a pelvic abscess and, rapidly, a generalized peritonitis. At a further laparotomy carried out three days after the first operation, a perforated gangrenous Meckel's diverticulum adherent to the pelvic adnexæ was found, arising from the ileum some 3 ft. from the ileo-cæcal valve.

The wall of the diverticulum, like the wall of the ileum from which it arises, contains an abundance of lymphoid tissue. Hyperplasia of the lymphoid follicles of the diverticulum has been found on histological examination of diverticula removed at operation from cases simulating acute appendicitis. It may be that increased tension within the diverticular wall produces pain through abnormal spasmodic ileal and diverticular movements. Whether the infection is viral in origin or an antigen–antibody response to infection elsewhere is unknown, but these cases, presenting with periumbilical colic and tenderness in the right lower quadrant of the abdomen, simulate closely acute appendicitis, though the most tender spot is rather closer to the umbilicus than McBurney's point (Aird, 1950). As a result of diverticular inflammation adhesions to adjacent structures occur

commonly with the production of sites of potential intestinal obstruction.

4. Tumours.—As described by Nygaard and Walters in 1937, both benign and malignant tumours arising in a Meckel's diverticulum remain pathological curiosities. Of the benign group, myoma, lipoma, neuroma, neurofibroma, and papilloma have all been described, as well as the group known as carcinoid tumours. In this series of 100 cases, 3 tumours of a Meckel's diverticulum were found. One, a lipoma, was previously reported by Foster in 1947. Arising in the submucosa, it had caused invagination of the diverticulum and an ileo-ileal intussusception. A second

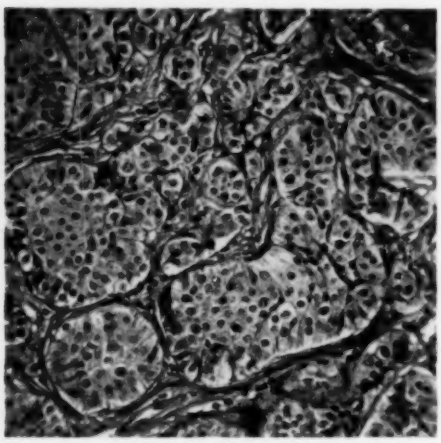


FIG. 447.—Carcinoid tumour, showing typical masses of polyhedral cells. H. and E. (× 150.)

FIG. 448.—Fibrosarcoma, showing elongated cells and occasional mitotic figures. H. and E. (× 150.)

case, a carcinoid tumour lying near the base of a diverticulum, was found at laparotomy for intestinal obstruction in a male aged 54 years (*Fig.* 447). These tumours arise from the Kultschitzky cells of the alimentary canal, which extended from the gastric cardia to the anus, and probably as a whole form part of an endocrine system secreting 5-hydroxytryptamine. Most commonly these tumours arise in the appendiceal region and in this site have relatively benign properties, metastasizing rarely (Moore, 1938), whereas extra-appendiceal tumours are multiple in 30 per cent, invade regional glands (40 per cent), and spread via the portal vein to the liver (Cooke, 1931; Dockerty and Ashburn, 1943). Masson recognized their affinity for silver stains, hence these tumours are known commonly as argentaffinomata.

Baird, Anderson, and Mills (1958) reviewed the recent literature, finding 13 cases of carcinoid tumour of a Meckel's diverticulum, and included a personal case, which presented incidentally at an operation carried out for carcinoma of the rectum. Of the 13 cases found, 12 occurred in males, and this was explained by the incidence of both Meckel's diverticulum and carcinoid tumours in general being greater in men.

The third tumour in this series was a malignant one and was found at laparotomy for generalized peritonitis. At operation a perforated fibrosarcoma of a Meckel's diverticulum was found (*Fig.* 448). There was no evidence of metastatic spread and the tumour was resected with a length of ileum. The patient, a man aged 74 years, did not survive the operation, dying of an overwhelming infection.

Moses (1947), in his authoritative review of 1605 reported cases of Meckel's diverticulum, found that malignant tumours were uncommon, occurring in 1·4 per cent (23 cases). Sarcoma is more common than carcinoma, though the number of reported cases remains small. Barrett (1954) recorded the nineteenth case of sarcoma of the diverticulum, and since that time at least 2 further cases have been recorded. The sex incidence of sarcoma is equal (9 males, 9 females, ? sex of 1 case), and this is unusual. Considering that Meckel's diverticulum occurs in males three or four times as commonly as in females, it would appear that there is greater tendency to sarcomatous malignant change in a diverticulum in women. Only 6 cases (0·37 per cent) of carcinoma of a Meckel's diverticulum were found by Moses, one of which arose in heterotopic gastric mucous membrane. Since this time at least one other case of carcinoma arising within Meckel's diverticulum has been described.

Malignant tumours of a Meckel's diverticulum have been discovered incidentally at post mortem, at operations for intestinal obstruction, or following perforation of a diverticulum. A palpable tumour can sometimes be made out in the right iliac fossa or in the pre-rectal pouch on rectal examination, but characteristically it is a mobile lump escaping from the examining hand.

Umbilical Symptoms.—A small number of cases of Meckel's diverticulum present with discharge of intestinal content at the umbilicus from birth; in these cases a patent omphalo-mesenteric duct has remained, uniting the ileum with the umbilicus. Occasionally this duct is so widely patent that prolapse of ileal mucosa occurs through the external opening, as occurred in this series in 2 cases. In both operation was carried out successfully. The umbilical discharge is rarely mucoid only, and bleeding may occur from

trauma to the delicate mucosa occasioned by the infant's clothing. In these cases the duct is not patent, but a small piece of ileal mucosa has become implanted at the umbilicus during the obliteration of the duct and it continues to secrete mucus; in those cases in which heterotopic gastric glands are present in this ectopic mucosa, gastric hydrochloric acid and pepsin are both secreted post-prandially.

DISCUSSION

Morphology.—Meckel's diverticula may appear in three main forms, accounting for 98·8 per cent of cases (Mason, 1936). The remainder include the rare giant diverticula and the umbilical polyps.

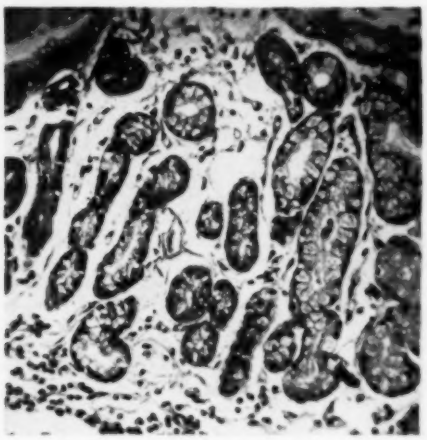


FIG. 449.—Heterotopic gastric mucous membrane. By the use of filters the eosinophilic oxyntic cells appear dark. H. and E. (× 150.)

1. The omphalo-mesenteric duct remains patent, accounting for 6·3 per cent of cases. This presents as the discharge of intestinal content at the umbilicus from birth and it may cause the prolapse of ileal mucosa externally.

2. Partial obliteration of the distal part of the duct may occur, leaving an ileal diverticulum attached to the umbilicus by a fibrous band, and this may produce intestinal obstruction. This is present in 10 per cent; the fibrous band may contain cystic remnants.

3. The typical diverticulum is present in 82·5 per cent. This appears as a cul-de-sac of the ileum. It may be conical or vermiform, approximating the appendix in appearance, or like the finger of a glove, and accessory sacculations may arise from it. Frequently the wall of these sacculations, unlike the Meckel's diverticulum, does not contain all the muscular layers of the ileum. Not infrequently a short mesentery to the diverticulum is present, but when truly antimesenteric in position the mesentery may be absent, the blood-supply to the diverticulum running in a band beneath the peritoneum transversely across the ileum.

Giant diverticula are extremely rare. Michel, Field, and Wogden (1955), when writing of a family of 4 cases of disease of a Meckel's diverticulum, record a case which at laparotomy revealed a large cystic mass some 17 × 24 × 4 cm., containing a litre of ileal content, and Yates (1930) reports the finding of an enormous cyst 56 × 17 × 5 cm., filling the whole abdomen. Gross (1953) regards these as cases of ileal duplication, though Michel and others suggest that these giant diverticula represent the persistence of the whole of the yolk-sac.

Meckel's diverticulum usually arises from the terminal ileum within 2–3 ft. of the ileo-cæcal valve. Considering its origin from the midgut of the embryo, it would seem possible that the diverticulum may arise from any part of the alimentary canal, the origin of which is from the embryo midgut, i.e., from the second part of the duodenum proximally to the mid-transverse colon distally.

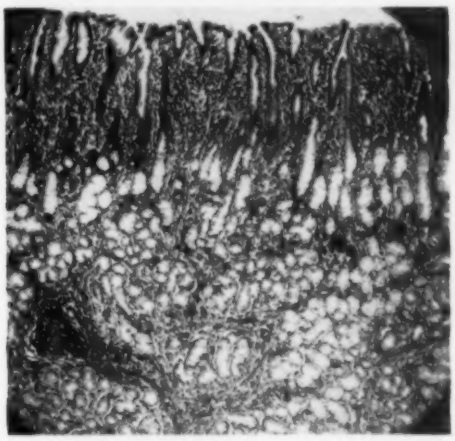


FIG. 450.—Heterotopic duodenal mucosa, showing typical Brunner's glands. H. and E. (× 42.)

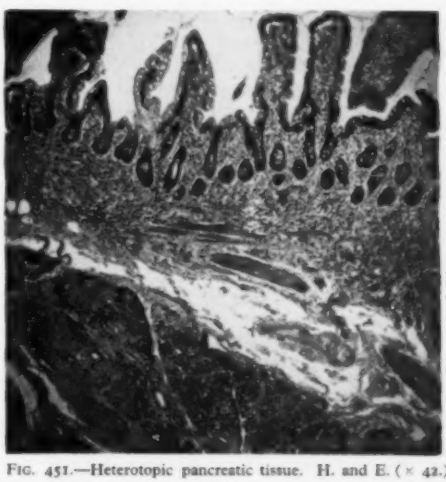


FIG. 451.—Heterotopic pancreatic tissue. H. and E. (× 42.)

Kiesewetter (1957) reports that 90 per cent occur within 100 cm. of the ileo-cæcal valve, but Doolin (1929) advised that at least 6 ft. of the ileum should

be searched to exclude the presence of a diverticulum. In this series all the diverticula arose from the ileum and within 100 cm. of the ileo-cæcal valve.

Heterotopia.—Normally the diverticulum is lined with ileal mucous membrane, but not infrequently mucosæ from other parts of the alimentary canal may be present. Most commonly gastric mucous

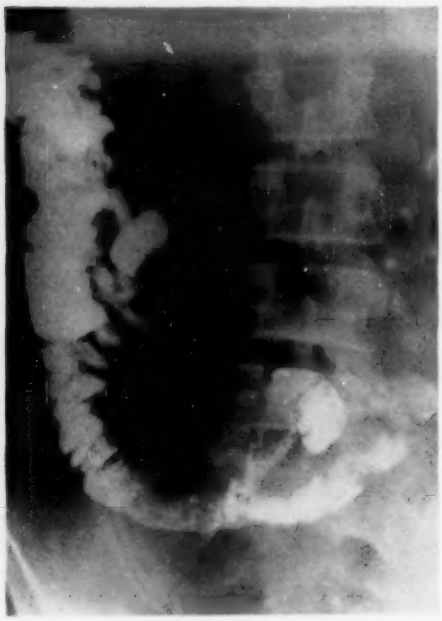


FIG. 452.—Meckel's diverticulum outlined with barium during follow-through procedure of barium meal.

membrane forms the aberrant lining (*Fig.* 449), and McParland and Kiesewetter (1958) found it present in 61 per cent of symptomatic cases. Rarely, duodenal (*Fig.* 450) or colonic mucosæ, or hepatic or pancreatic (*Fig.* 451) parenchyma may be present. There are three main hypotheses concerning the reasons for heterotopia. Albrecht (1901) and Card and Mimpriss (1937) reason that the lining of the embryo midgut and omphalo-mesenteric duct is totipotent, and therefore has the capability of developing into any of the digestive epithelia found in or arising from the embryological midgut.

The stomach, however, is a foregut derivative and heterotopia in the ileum is rare, except possibly at the base of a Meckel's diverticulum. Farr and Penke (1935) suggest that the omphalo-mesenteric duct is lined by cells which even in the 5–7-week-old embryo have a secretory and digestive function, enabling yolk-sac contents to be metabolized. Yolk-sac contents, however, supply nutriment to the embryo from the eleventh to the eighteenth day only; after this time the yolk-sac subserves an erythropoietic function solely. Furthermore, zymogen granules have not been demonstrated in the omphalo-mesenteric duct. Schaetz (1925) thinks that a migration of cells along the primitive gut occurs with reimplantation at sites of narrowing (cardia, duodenum, and the obliterating omphalo-mesenteric duct), accounting for heterotopia at these sites. But heterotopia does not occur at the duodeno-jejunal flexure, ileo-cæcal valve, or the rectosigmoid junction, though these too are narrow parts of the alimentary canal. It would appear that none of these ideas explains completely the presence of heterotopic tissue in a Meckel's diverticulum.

Diagnosis.—Mayo wrote in 1933: "Meckel's diverticulum is frequently suspected, often looked for and seldom found." While it is true that they are seldom found, all too infrequently are they sought, and the pre-operative diagnosis of a Meckel's diverticulum is rarely made, other than in children presenting with intestinal hæmorrhage, as there is an absence of specific symptomatology (Sneierson, 1950).

Gross (1953) states that barium studies of the small intestine for Meckel's diverticulum are useless. Stein, Bennett, and Finkelstein (1958) recorded 33 cases of recognition of a Meckel's diverticulum during barium series and reported 4 personal cases. It must be admitted that the results of routine barium follow-through examination of the small intestine for demonstrating diverticula are very poor, and though barium may reflux into the terminal ileum during a barium enema, outlining a diverticulum, the finding of a diverticulum is usually fortuitous. In this series the diverticulum was recognized in 2 patients during the follow-through procedure of a barium meal, and one of the plates is reproduced in *Fig.* 452. The use of the 'small bowel enema' (Schatzki, 1943) and the 'iced water' technique (Weintraub and Williams, 1949), with abdominal compression and frequent screening, are of value in examining accurately the mucosal pattern and, possibly, diverticula of the small intestine. Their wider use in suspected cases of disease of a Meckel's diverticulum may lead to an increase in pre-operative diagnosis of its presence.

Treatment.—While it is agreed that many people with a Meckel's diverticulum of the ileum live healthy, normal lives, there can be no doubt that with the onset of complications, life is in jeopardy. The question of the removal of the 'normal' diverticulum found incidentally at laparotomy remains one of debate, though most surgeons stress the necessity of its routine removal (Greenblatt and others, 1936). The mortality following its removal in 58 children was 3·6 per cent (McParland and Kiesewetter, 1958) and the deaths which occurred were due to severe complications in symptomatic cases, whereas in the cases found incidentally, removal did not increase the morbidity of an exploratory laparotomy. Of 48 cases in which at laparotomy a Meckel's diverticulum was found but not removed, 8 required subsequent laparotomy for the removal of the diverticulum because symptoms persisted (Wansborough, Thompson, and Lecky, 1957). Furthermore, the diverticulum which macroscopically appears to be normal, may yet be the cause of the symptomatology (Wagner, Shallow, and Eger, 1950).

Considering these features, there can be little disagreement that all Meckel's diverticula should be removed. The crush ligature technique, as in appendicectomy, is not applicable here, and the removal of the diverticulum alone is not enough. It

is recommended that a cuff of ileum should be resected with the diverticulum, in order that the ulcer-bearing area is removed completely, and to avoid narrowing of the lumen of the bowel.

SUMMARY

One hundred cases of Meckel's diverticulum have been reviewed, confirming that disease of the diverticulum has no specific symptomatology and affects all age-groups.

The mode of presentation is described with a discussion of the theories of heterotopia and a description of morphological types. It is suggested that the more widespread use of the new radiological techniques for demonstrating abnormalities and diseases of the small intestine may be of value in revealing the presence of a Meckel's diverticulum.

Excision of all Meckel's diverticula discovered at operation, whether obviously the cause of disease or incidental findings, is recommended.

I am indebted to Professor Lambert Rogers, the Consultant Surgeons of the United Cardiff Hospitals, and to Mr. Melbourne Thomas, of the East Glamorgan Hospital, for permission to publish details of these cases.

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THE SEAT OF UNCONSCIOUSNESS IN HEAD INJURIES

A STUDY BASED ON FIFTY NECROPSIES

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Since the outstanding feature of a closed head injury is unconsciousness, it is of interest to inquire whether or not this state is due to paralysis of function of one particular part of the brain concerned with awareness. The problem of differing depths of unconsciousness can, to some extent, be accounted for by differing degrees of damage to the same neurones. For many reasons it has become customary to regard paralysis of function of the upper brain-stem mechanisms as the main cause of unconsciousness in neurological disorders. Certainly, the overall experience of neurology supports this belief, as the writings of Penfield and Erickson (1941), Penfield and Rasmussen (1950), Penfield and Jasper (1954), and Jefferson (Jefferson, 1944; Jefferson and Johnson, 1950) clearly show. Also, the experimental work of Denny-Brown and Ritchie Russell (1941) points to the brain-stem as the probable anatomical substratum of concussion, as does the work of Magoun (1952a, b; 1958) and Moruzzi (Moruzzi and Magoun, 1949; Moruzzi, 1954) on the reticular system. Also, I would like to call attention to a Symposium issued by the Council for International Organizations of Medical Science on "Brain Mechanisms and Consciousness" (1954). Recently the arguments relating to the brain-stem and unconsciousness have been exhaustively and succinctly set out by Feldberg (1959).

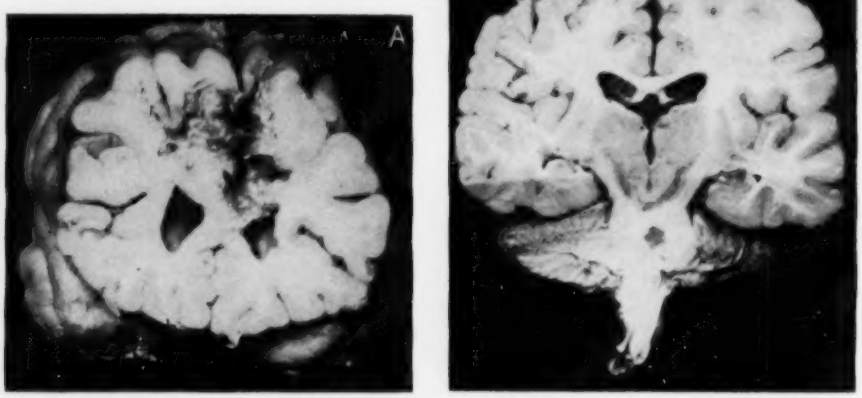

Fig. 453.—When physical damage is demonstrable in the brain-stem the hemispheres are usually severely contused or lacerated.

None the less, with a full appreciation of the part the brain-stem plays in consciousness and sleep, I will endeavour to show that unconsciousness in closed head injuries commonly results from paralysis of function of the neurones of the hemispheral cortices and of their tracts above the brain-stem and basal ganglia. In simple terms, my thesis may be summarized as brain-stem versus hemispheral concussion.

MATERIAL

The material on which this work is based consists of a series of 50 brains taken at autopsy from patients who had died as the result of a closed head injury. The histories and clinical details were known in each case.

The procedure of examination of each specimen was as follows:—

1. The brain, including the upper part of the spinal cord, was removed either within or without the dural envelope, according to the presence or not of an extradural hæmorrhage. Surface hæmorrhages, lacerations, and contusions were described and photographed.

2. Before hardening, the brains were cut in the coronal plane, particular care being taken with those slices that passed through the brain-stem and basal ganglia. Detailed photographic records were made of each slice.

3. Each slice of brain was hardened in 10 per cent formalin and, after the usual preparations, embedded in wax and cut on a large microtome. Though complete serial sectioning, for obvious reasons, was not carried out, very large numbers of sections were made at such distances that it was unlikely that significant lesions would be missed.

The following methods of staining were used: (1) Eosin and hæmatoxylin; (2) Van Gieson; (3) Nissl.

PATHOLOGICAL FINDINGS

In 4 cases only out of the total 50 was damage of macroscopical dimensions found in the brain-stem; and in each of these 4 cases there was severe concomitant damage in the cerebral hemispheres (*Fig.* 453). Gross damage within the cerebellar hemispheres was not found in a single specimen. In no case was the surface of the brain-stem or cerebellum lacerated. Close to the site of naked-eye damage within the

brain-stem small areas of gross damage could be detected by the microscope, but these petechiæ were nothing like so numerous or widespread as those found in the cerebral hemispheres. Gross brain-stem damage detectable only by the microscope was found in 2 more cases. Thus, out of a total of 50 cases, 6 only showed evidence of damage that could be detected either by naked eye or by the microscope.

On the other hand, in all of these 50 cases the cerebral hemispheres were invariably contused or lacerated. Also, intracerebral hæmorrhages of varying dimensions were usually present. Indeed, the relative degree of damage within the cerebral hemisphere and the brain-stem, severe in the hemispheres and relatively mild in the brain-stem, was most striking (*Fig.* 454). Also, whereas surface hæmorrhages of the subarachnoid and subdural types were almost invariably found over the cerebral hemispheres, extravasations of blood were relatively rare in the posterior fossa (*Fig.* 455).

These findings form the major part of my thesis and I believe the evidence is convincing.

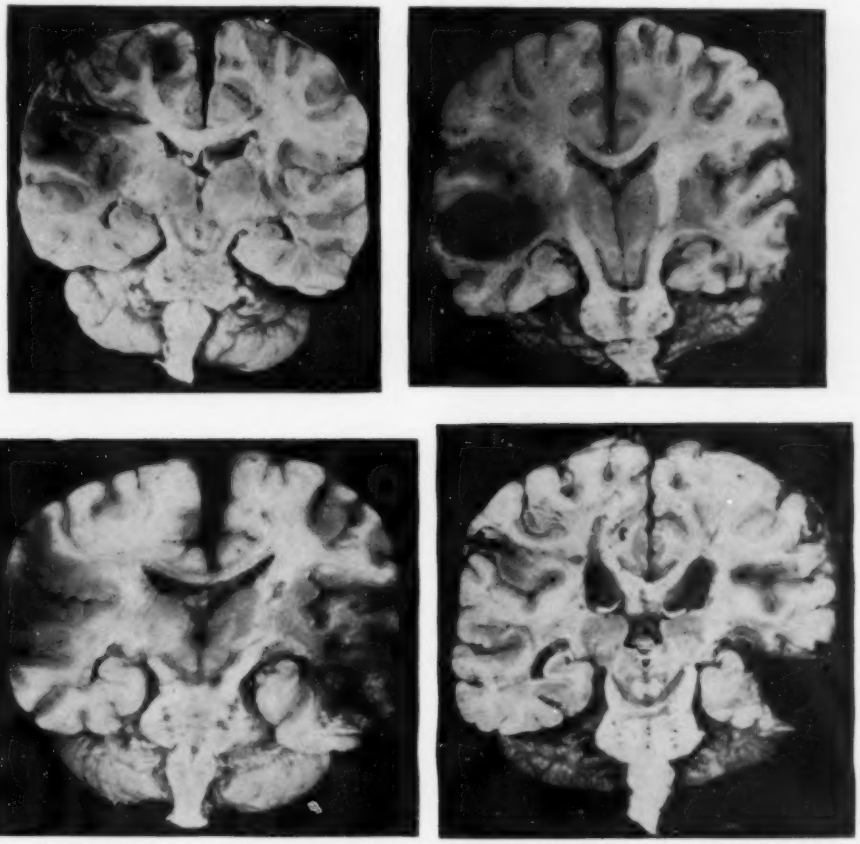

FIG. 454.—Severe hemispheral damage of macroscopical dimensions is commonly found with the brain-stem intact, as illustrated by the above four photographs.

Certain other features, however, stood out and a note of them is made because of their particular interest.

1. Corpus Callosum.—One outstanding feature of this subsidiary study was the frequency and extent of damage to the corpus callosum (*Fig.* 456). What such damage means in terms of neural dysfunction can only be a matter of speculation, but at least it would not be unreasonable to suggest that it was important in producing hemispheral dysfunction.

2. Cerebral Œdema.—A great deal of controversy exists in pathological circles on the role that cerebral œdema plays in the acute phases of a head injury. That it can occur in significant degree both generally and locally is illustrated in *Fig.* 457. However, in relation to contusional and hæmorrhagic lesions it was relatively unimportant and rare.

3. Surface Hæmorrhages.—Extensive hemispheral subarachnoid and subdural bleeding was invariably present. In the subarachnoid space blood rarely collected in such masses as to compress the brain, but could obviously obstruct the free flow of

cerebrospinal fluid. On the other hand, subdural collections of blood, sufficient to disturb the position of the lateral ventricles of the brain, were by no means uncommon. Their size and surgical significance were clearly shown in 4 cases where the brain had been removed and hardened in its dural envelope. Indeed, this study emphasizes the importance of subdural hæmorrhage in acute head injuries and points to the value of early burr-hole drainage (*Fig.* 458).

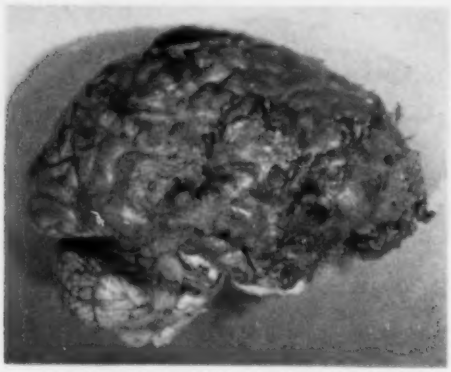

FIG. 455.—A severe laceration of the cerebral hemispheres with the posterior fossa brain contents virtually intact.

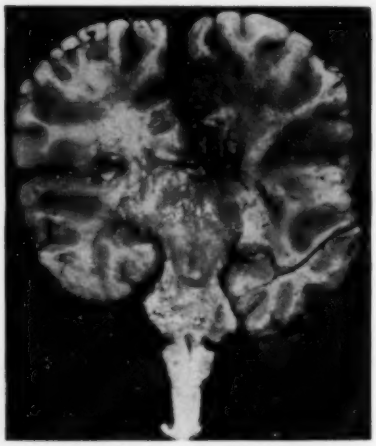

FIG. 456.—Damage of corpus callosum was a common feature in this series.

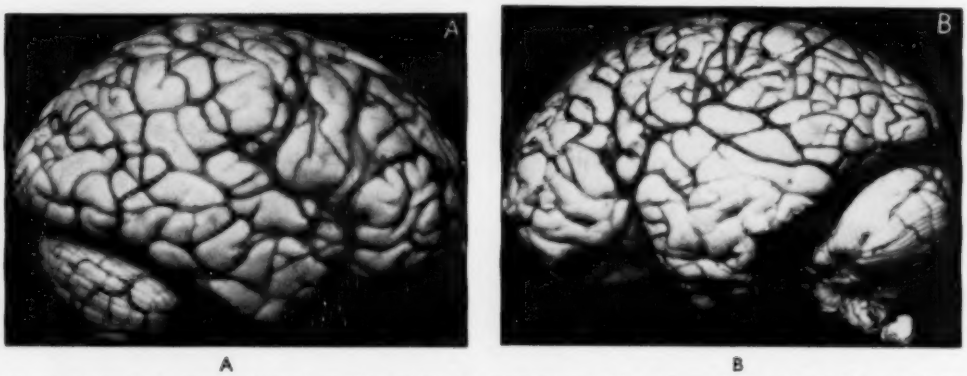

FIG. 457.—Œdema of the brain in the acute stages of a head injury occasionally occurs either widespread (A), or focally (B), to complicate the clinical picture of concussion.

Massive extradural hæmorrhages are occasionally found in those cases where there has been no latent interval and in this series occurred in 2 cases (*Fig.* 459). Thin layers of blood in the extradural space, on the other hand, were of common occurrence and possibly, though not compressive in degree, could well account for prolonged head pain in patients who survive and in whom they presumably occur. Unlike subdural hæmorrhages, which normally remain fluid for long periods and can be drained through local burr holes, extradural hæmorrhages rapidly become gelatinous and can only be adequately removed by radical exposure.

Whatever the submicroscopical degrees of damage in acute head injuries might be—and these certainly must be extensive—the gross hæmorrhagic lesions are so common that surgical supervision in all serious head injuries is important.

COMMENTS AND CONCLUSIONS

There are three degrees of injury which may produce paralysis of function of nervous tissue—macroscopical, microscopical, and submicroscopical. From a study of macroscopical lesions seen at autopsy it is obvious that the size and position of the contusions, lacerations, and hæmorrhages will often not account for the associated clinical picture. Therefore, and with reason, it is customary to attribute the complex clinical picture of unconsciousness and abnormal movements and postures to damage of microscopical and submicroscopical dimensions in areas of the brain primarily concerned with consciousness and integration of movement. Of these two minor degrees of injury, submicroscopical, rather than microscopical, damage is more often invoked as the cause of concussion. Indeed, a great deal of necropsy evidence has amassed to show that

major losses of function in many cases of closed head injury must be due to neuronal damage of hidden dimensions. Here I would like to call attention to an excellent monograph by Courville (1953) in which is set out a clear, well-balanced, and comprehensive history of concussion.

There is no doubt whatever that damage to the brain-stem alone can cause unconsciousness. For a patient to be conscious his brain-stem must be alive and functioning. Having granted this essential role that the brain-stem plays in consciousness, it is now necessary to inquire what role the cerebral hemispheres play. Though one cerebral hemisphere can be removed surgically and the patient remain conscious, there is no proof whatever that both hemispheres can be removed without impairing consciousness. Indeed, it is my thesis that if there is complete neuronal paralysis of both hemispheral cortices, or tracts within the hemispheres, then unconsciousness must occur. Otherwise we must accept that a high brain-stem preparation, without the aid of the hemispheres, can be fully aware of itself and its environment; a proposition which to me is unacceptable. According to latest neurological theory, the brain-stem is an integrating centre, and to function properly, I believe, must have something to integrate. Surely also if it is the arousal centre, it must have something to arouse. Consciousness, I suggest, must depend both on an alive, active brain-stem and on concomitantly alive and active hemispheres. Paralysis of function of either, or both, leads to unconsciousness.

In many cases of head injury reaction of the pupil to light, dependent on a brain-stem mechanism, remains, whereas the reaction to frightening gestures, dependent on hemispheral circuits, are in abeyance, which points to hemispheral rather than to brain-stem paralysis.

If we accept, and the author must, that complete bilateral hemispheral cortical paralysis produces unconsciousness, it still remains necessary to consider whether, in closed head injuries, the relevant damage occurs in the hemispheres, in the brain-stem, or both. In this series there were 6 instances of macroscopical damage within the brain-stem. But in all these cases there was also evidence of severe hemispheral damage amounting at times to virtual disintegration. Areas of microscopical damage were commonly seen scattered within the cerebral hemispheres. On the other hand, areas of microscopical damage within the brain-stem were uncommon. Circumscribed lesions within the reticular area of the brain-stem were conspicuous by their absence.

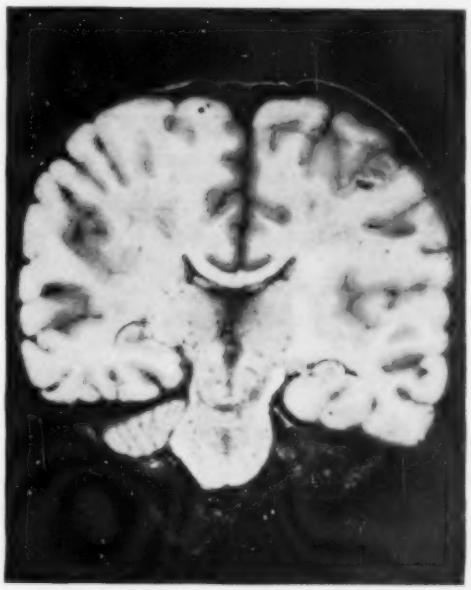

FIG. 458.—Subdural hæmatomata remain fluid for long periods and can be adequately drained through burr-hole exposures.

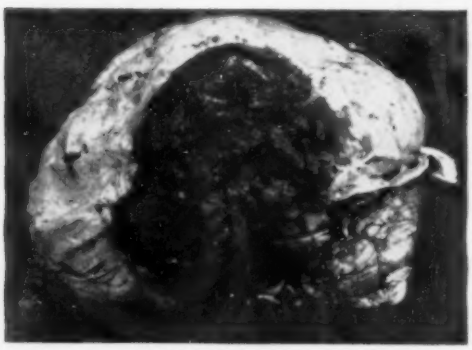

FIG. 459.—Extradural hæmatomata are typically of this size and shape. They rapidly become gelatinous and are best dealt with surgically through a wide exposure.

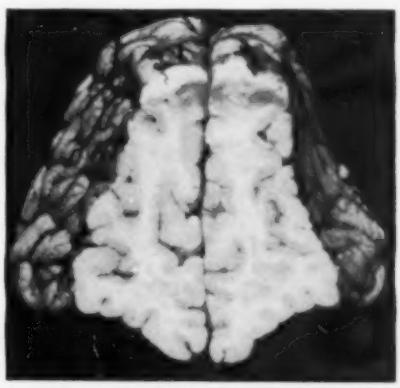

FIG. 460.—Severe hemispheral atrophy is by no means rare as the result of closed head injuries.

In the majority of cases the macroscopical damage to the hemispheres was severe, whereas the brain-stem looked unscathed.

Therefore, since in closed head injuries the hemispheres are liable to receive greater macroscopical and microscopical damage than is the brain-stem, it is reasonable to suggest that they also come in for more damage of submicroscopical dimensions. In other

words, the forces that cause concussion must show a greater tendency to paralyse the hemispheres than the brain-stem (*Fig.* 460).

And, if we accept that bilateral hemispheral neuronal paralysis can cause unconsciousness, then hemispheral must be more frequent than brain-stem concussion.

Finally, I would like to refer you to the classical work carried out by Sabine J. Strich (1956) in the Oxford School of Neurological Surgery on the severity of hemispheral damage that occurs in some cases of prolonged unconsciousness.

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LIVER FLUKE INFESTATION AND CHOLANGIO-HEPATITIS

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CHOLANGIO-HEPATITIS occurs in recurrent attacks due to intrahepatic and extrahepatic stones usually with obstructive jaundice. It is prevalent among the Chinese community in Hong Kong and natives of the South-eastern Asian countries. It was first recognized by Digby (1930) and later studied by Cook, Hou, Ho, and McFadzean (1954) and by Stock and Tinckler (1955). While the clinical picture and the pathological features are fairly typical and well recognized, the aetiology is still far from being fully understood. Furthermore, owing to the endemicity of the condition long-term experience in the management of the disease is still lacking. This communication is based upon the author's own observations of 242 cases admitted to the University Surgical Professorial Unit and from personal experience in dealing with 96 cases of the same series.

Table I.—DISEASES AFFECTING THE BILIARY SYSTEM (July, 1948–December, 1958)

Disease		*No. of Cases*
Cholangio-hepatitis		242
Cholelithiasis		178
Cirrhosis of liver		55
Carcinoma of liver	primary	21
	secondary	4
Carcinoma of pancreas		8
Pancreatitis	acute	7
	subacute	3
	chronic	3
Ascaris in common bile-duct		7
Carcinoma of common bile-duct		3
Carcinoma of gall-bladder		4
Liver abscess	pyogenic	4
	amœbic	4
Non-parasitic cyst of liver		5
Traumatic rupture of liver		3
Typhoid carrier		2
Infectious hepatitis		3
Stricture of common bile-duct		3
Choledochus cyst		3
Schistosomiasis of liver		1
Hæmangioma of liver		2
Gumma of liver		1
	TOTAL	566

INCIDENCE

Among the 13,868 admissions from 1948 to 1958, there were 566 patients with diseases of the biliary system, of whom 242 were suffering from cholangio-hepatitis. All were Chinese. None has been seen in a European (*Table I*).

Cholangio-hepatitis affects all ages, from 3 years to 72 years in our series, the peak incidence being in the third and fourth decades. It also affects both sexes equally. It is interesting to note that even for simple cholelithiasis in Chinese, the age incidence is found at a slightly younger level than elsewhere and the sex incidence is, in our experience, equal (*Figs.* 461, 462).

SYMPTOMATOLOGY

The acute attack presents as an acute abdominal emergency referable to the biliary system. The main features are pain, fever, jaundice, and a history of previous attacks of similar nature (*Table II*).

Pain is by far the most important and consistent complaint that brings the patient to the hospital. It occurs in all the patients at some time in the course

of the disease. It may commence suddenly, but is not infrequently preceded by mild epigastric discomfort and anorexia. It is at first colicky in nature, felt in the epigastrium or right upper quadrant. Later it becomes

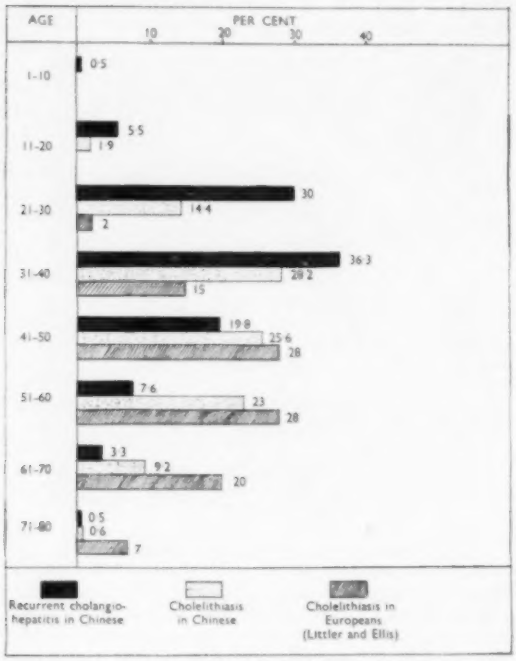

FIG. 461.—Age incidence.

volunteered. At the height of the attack, nausea and vomiting may be experienced.

Fever was present in 48·7 per cent of the cases, typically 'spiky' in character (*Fig.* 463), and associated with chills and sometimes rigors. It is seen usually in patients 48 hours or longer after the onset of pain. Patients who come for treatment within 24–48 hours of the onset of pain are usually afebrile.

Jaundice occurred in 53·7 per cent of patients. It usually appears 1–2 days after the onset of pain. In

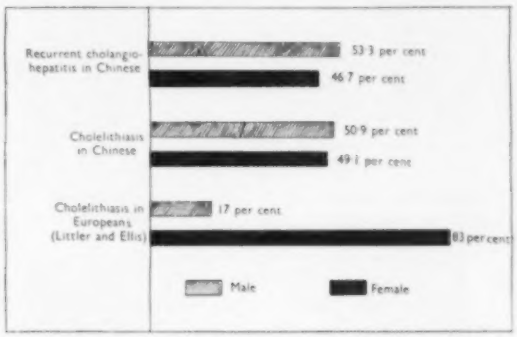

FIG. 462.—Sex incidence.

mild cases or in cases in which obstruction is limited to the intrahepatic biliary tract, no jaundice is observed, but laboratory investigation reveals an elevation of icteric index and serum-bilirubin concentration.

It is our policy to operate on patients with acute gall-bladder disease as an emergency measure soon after admission and assessment. This explains the

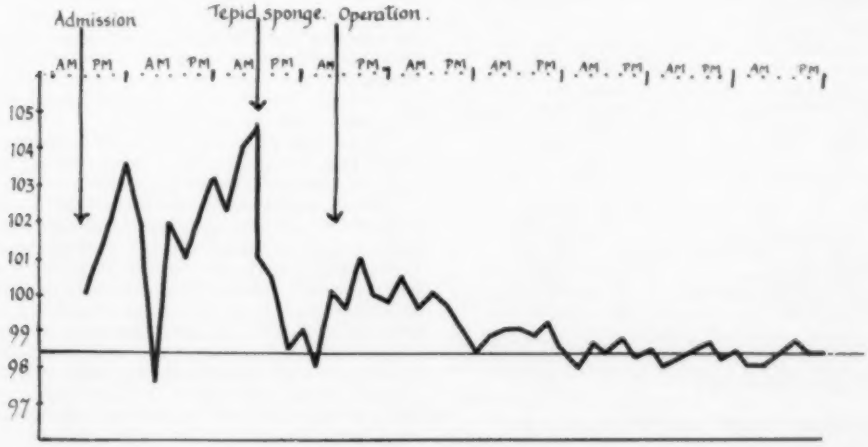

FIG. 463.—Temperature chart.

severe, lancinating, and persistent, lasting for a few minutes to a few hours. It may occasionally radiate to the back or to the tip of the right shoulder. Flatulence is not usually complained of, though, rarely, a history of intolerance to fat may be

relatively low incidence of fever and jaundice in this series.

A *history of recurrence* was obtained in 71 per cent of the cases, sometimes repeatedly over a period of 10 years. This can be explained by the fact that

smaller stones coming down from the intrahepatic ducts may pass into the duodenum after one attack of colic. Alternatively, a stone in the common bile-duct may exert a ball-valve mechanism with intermittent obstruction. Still another group of patients may have stones packed tightly in an enormously dilated common bile-duct without any alarming symptom except occasional and transient epigastric discomfort, regarded by the patients as indigestion.

Table II.—SYMPTOMATOLOGY IN 242 PATIENTS

Symptom		*No. of Patients*	*Percentage*
Abdominal pain	colicky	200	82·6
	dull-aching	40	16·1
Referred shoulder pain		5	2
Fever		118	48·7
Chills and rigor		48	20
Jaundice		130	53·7
Nausea and vomiting		150	61·5
Bowel constipation		88	36·3
Fat intolerance		15	61·5
History of recurrence		172	71
Dark urine (subjective)		145	60
Pale stool (subjective)		4	1·6

PHYSICAL SIGNS

With very few exceptions, the patients are malnourished, with hæmoglobin of 10·5 g. per cent and serum-protein 5·8 g. per cent in the average. These figures could be much lower as there is usually dehydration with hæmoconcentration as a result of repeated vomiting. During the attacks the patient appears to be toxic and in pain. Jaundice, when present, ranges from slight yellow discoloration of the sclera to a greenish-brown hue of the skin. A very constant finding is tenderness and muscle-guarding in the epigastric region, right upper quadrant, and sometimes right lower quadrant of the abdomen. The liver and gall-bladder were enlarged, palpable, and tender in 32 per cent and 30 per cent of cases respectively. A much higher incidence (82 per cent) of enlarged gall-bladder was found when the patients were under anæsthesia and when the abdomen was opened, as muscle-guarding prevents its detection clinically. Courvoisier's law obviously is not applicable in these cases.

Table III.— PHYSICAL SIGNS

Signs	*No. of Patients*	*Percentage*
Tenderness and guarding in right upper quadrant	213	88
Palpable liver	78	32·2
Palpable gall-bladder	73	30·1
Positive Murphy's sign	41	17
Palpable spleen	10	4·1

The spleen was palpable only in a small percentage of cases (4 per cent) and evidence of portal hypertension is rare (*Table III*).

LABORATORY INVESTIGATION

Mild leucocytosis (10,000–15,000 per c. mm.) is detected in a majority of cases. The urine contained bile in 74 per cent of cases and increased urobilinogen in 85 per cent of cases. The van den Bergh reaction usually shows a direct positive result with increased serum-bilirubin of 2–7·5 mg. per cent. Serum alkaline phosphatase is increased to around 15–20 K.A. units. Cephalin flocculation and thymol turbidity usually show moderate impairment of liver function. The blood-cholesterol level is usually around 200 mg. per cent.

In almost all cases of cholangio-hepatitis proved by laparotomy, *Clonorchis* ova are found either in the stool or in the bile. The stool was coloured in all except 4 cases in which jaundice had persisted for over 2 weeks.

Radiography occasionally shows a shadow in the right upper quadrant due to stones in the gall-bladder or the common bile-duct. The incidence was, however, rather low (27 per cent). The typical ring-shaped appearance or faceted stone shadow is rare. The stones, if radiopaque, appear as homogeneous shadows of moderate density and may be mistaken for fæcal matter (*Figs.* 464, 465).

Occasionally gas is seen in the biliary tree, not due to formation of biliary-enteric fistula but to the presence of a gas-forming organism.

Oral cholecystography and intravenous cholangiography, even in the absence of jaundice, almost always fail to visualize the gall-bladder or the biliary tree (95 per cent of non-visualization). This, in correlation with the operative and pathological findings, suggests hepatic and gall-bladder functional impairment. These patients require large amounts of curare during anæsthesia because of the reduced production of pseudo-cholinesterase by the damaged liver.

PATHOLOGY

On laparotomy, some degree of localized peritonitis is encountered with adherent omentum, bile-stained exudate, or even fibrous adhesions obliterating the right inferior subphrenic space. These adhesions, however, can be separated easily, and access to the gall-bladder and the free edge of the lesser omentum can be established without difficulty.

The liver was enlarged and congested in 85 per cent of cases, with typically dilated bile canaliculi seen on the surface. Multiple liver abscesses of various sizes may be found (4 cases), and in 1 case a left subphrenic collection of bile-stained fluid and pus was present, presumably owing to rupture of dilated bile canaliculi or of an abscess.

When adequate and prolonged drainage of the biliary tree is instituted, the dilatation of the canaliculi subsides, as may be seen at subsequent re-exploration.

Stones may be palpable in isolated areas of the liver, with a grating sensation. On casual palpation these may be mistaken for carcinomatous growths. In some cases a large area of the liver is replaced by markedly dilated and tortuous bile-ducts with intrahepatic stones. In one case the left lobe of the liver was replaced by a huge cavity containing bile-stained pus, biliary mud, and numerous stones of melon-seed appearance. This cavity after incision and drainage yielded about 350–500 c.c. of bile daily until the common bile-duct was explored, intraductal stones were removed, a stricture in the left hepatic duct was dilated, and a choledocho-duodenostomy performed.

Gross cirrhosis of the liver was found in 5 cases and cholangioma in 3 cases.

The gall-bladder was tensely distended in 80 per cent of cases and its wall much thickened and œdematous. In 10 per cent of cases the gall-bladder

was gangrenous, with localized peritonitis near Hartmann's pouch. Stones of various sizes were palpable or later recovered in 20 per cent of cases, the larger ones of an earthy character. Frequently living or dead and calcified *Clonorchis* adult worms together with biliary mud and debris are found in the

FIG. 464.—Straight radiograph of right upper quadrant of abdomen showing stone shadow and gas in biliary tract.

gall-bladder, and microscopical examination of the organ invariably shows chronic inflammatory changes of the wall with acute foci.

The free edge of the lesser omentum is usually thickened and œdematous. On incising it, the common bile-duct was found to be œdematous and distended in 85 per cent of cases, with dilated lymphatics on the surface and stones palpable in the lumen. In some cases it measures over 2–3 cm. in diameter. One or two enlarged lymph-nodes are frequently present in the supraduodenal region.

The wall of the common bile-duct is almost always thickened and the intimal surface roughened. The content of the duct varies from slightly turbid bile with *Clonorchis* worms and debris to thick purulent and fæcal-smelling bile or frank pus. Stones of various sizes were present in over 50 per cent of cases. Some of the stones measure 5 × 3 cm. and have to be removed piecemeal, being soft and muddy. When dry, they are friable, flaking off in layers easily. They are brownish-yellow in colour, with occasionally a dark-pigmented outer coating—the earthy stone of Aschoff. The centre may be formed by a disintegrated *Clonorchis* worm. Rarely the centre is formed by a cholesterol nucleus. The main component is calcium bilirubinate.

Culture of the bile from the common bile-duct revealed the presence of either *Esch. coli* or anaerobic streptococci, or both, in 76 per cent of cases. The remaining 24 per cent yielded sterile bile in spite of the fact that large stones were present in the common bile-duct or intrahepatic ducts.

The hepatic ducts on exploration are usually found to be dilated as far as the stone forceps can reach and contain various numbers of stones or *Clonorchis* worms. Definite strictures are also encountered, more commonly on the left side. When the stricture is dilated by graduated bougies, the duct proximal to it is found to be markedly distended with biliary debris, stones, and sometimes pus. This

FIG. 465.—Photograph of stone removed from patient.

FIG. 466.—Post-operative cholangiogram showing stricture formations in both hepatic ducts. The stricture is usually proximal to the bifurcation of the ducts. A residual stone is present in the common bile-duct.

stricture formation can also be demonstrated in post-operative cholangiograms (*Fig.* 466).

The common bile-duct is dilated in both supra-duodenal and retropancreatic portions, tapering off abruptly at the sphincter of Oddi, which is almost always closed but patent, yielding to the passage of graduated bougies readily. Definite stenosis at the sphincter was demonstrated in only 5 cases. Slight œdema of the duodenal mucosa at the papilla may be seen on transduodenal exploration.

The head of the pancreas may be indurated and nodular (5 per cent), but evidence of acute pancreatitis has never been found.

The spleen was enlarged only in 5 cases associated with portal hypertension.

In 6 patients there was concomitant peptic ulceration of the stomach which required surgical treatment.

Biopsy of the liver reveals most interesting features. There is almost always marked increase of periductal fibrous tissue and cellular infiltration in the portal space. The biliary ductules are increased in number, dilated, and filled with desquamated epithelial cells, inflammatory cells, and occasionally

Clonorchis ova or adult worms. There may be some degree of adenomatous formation of the epithelium typical of clonorchiasis of the liver. The intercellular bile canaliculi are also increased in number and are distended by bile. Fatty degeneration of the liver cells is evident. All these changes are patchy and scattered in distribution, corresponding to the gross appearance seen during operation.

Biopsy of the common bile-duct reveals disruption of the epithelial lining with extensive fibrous tissue formation and absence of musculature in the wall. In some long-standing cases cartilage cells are present in the wall presumably owing to metaplasia of the fibrous tissue in response to chronic irritation.

Biopsy of the sphincter of Oddi shows a normal or moderately increased amount of sphincteric muscle and moderate cellular infiltration. There is no obvious increase of fibrous tissue formation in the submucosal layer.

DISCUSSION

Moynihan stated that gall-stones were tombstones erected to the memory of dead bacteria. Ogilvie (1957) believes that the common mixed gall-stones are the price we pay for contentment, prosperity, and good living. But here in Hong Kong we have cholangio-hepatitis associated with ductal stones which are not of gall-bladder origin, and are certainly not the result of luxurious living. It is difficult to be dogmatic as to whether the intrahepatic stones are the cause or the effect of pyogenic infection of the biliary tract. Cook and others (1954) are of the opinion that they are purely of infective origin and are strongly in favour of Moynihan's aphorism. It is, however, difficult to explain some of the facts which we have observed. There were cases in which stones were found in both intrahepatic and extrahepatic ducts with no concomitant clinical signs or pathological changes of inflammation of the biliary system. Culture of the bile from these cases also revealed no bacterial growth. There were other cases in which only *Clonorchis* worms were found in the intrahepatic and extrahepatic ducts with sterile bile, yet producing typical symptoms and signs of cholangio-hepatitis. Drainage of the common bile-duct in these cases, however, later yielded biliary mud, debris, and calcium bilirubinate crystals suggesting intrahepatic obstruction by stones.

Table IV.—Frequency of Parasitic Infestation

Number of positive findings of parasitic ova in stool in a series of 2539 Chinese surgical patients

Parasites	*No. of Patients*	*Percentage*
Clonorchis sinensis	1159	45·6
Trichuris trichiura	799	31·5
Ascaris lumbricoides	467	18·4
Ankylostoma duodenale	266	10·5
Fasciolopsis buski	28	1·1
Enterobius vermicularis	7	0·2
Negative findings	676	26·6

It is, therefore, feasible to postulate that intrahepatic stones, perhaps of microscopic size (bile thrombi), may be the initial lesion leading to the pathological changes and the clinical syndrome.

This leads to a discussion of the aetiology of intrahepatic stone formation in this condition, and it seems reasonable to relate these changes to infestation with *Clonorchis sinensis* for the following reasons:—

1. Geographic distribution: Clonorchiasis is an endemic disease of South-East Asia. This corresponds to the distribution of cholangio-hepatitis as reported by various authors (*Fig.* 467 and *Table IV*).

2. In a high proportion (91 per cent) of our patients suffering from cholangio-hepatitis, *Clonorchis* infestation could be demonstrated either by the presence of adult *Clonorchis* worms or ova in the bile at laparotomy or by the discovery of ova in the stool. Failure to demonstrate *Clonorchis* worms or ova either in the bile or in the stool still does not rule out infestation, since, as pointed out by Hou (1955), *Clonorchis* may die in the presence of pyogenic infection. Many of the stones actually have the shape of *Clonorchis* adult worms (*Fig.* 468).

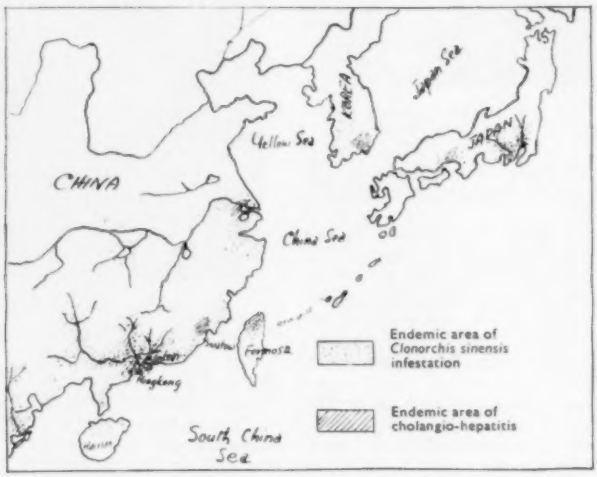

Fig. 467.—Map showing geographic distribution of *Clonorchis sinensis* infestation and of cholangio-hepatitis.

3. In chronic clonorchiasis the liver is slightly enlarged pathologically. The affected ducts are well defined and slightly thickened. Localized dilatation of the bile-ducts, usually near the free edge of the liver, especially in the left lobe, is evident, giving rise to a varicose appearance in severe cases. Atrophy of the liver tissue is also present around the affected ducts near the serous surface. In places stricture formation is found with market dilatation of the duct peripheral to it, containing debris.

Microscopically, the epithelial lining of the ducts may desquamate partly or completely, or may be preserved and thrown into folds, or may show adenomatous formation. There is usually abundant connective-tissue formation in the wall of the ducts and in the portal space.

Excessive glue-like mucinous material is found both in the epithelial cells and in the lumen of the ducts, which conglomerates the *Clonorchis* ova or disintegrated adult worm, and the desquamated epithelial cells, to form bile thrombi or stones.

This pathological picture is very much akin to that found in cholangio-hepatitis. In the latter, additional inflammatory changes such as cellular infiltration and abscess formation are also present.

4. This particular syndrome is not found in countries other than those infested by *Clonorchis*. Nor is it found in Europeans residing in Hong Kong, in whom no evidence of infestation is found.

With the pathological changes in the liver due to clonorchiasis as a background, it is not difficult to postulate the mechanism of formation of intrahepatic stones and to explain the frequent occurrence of pyogenic infection of the biliary tree. As a result of the thickening of the wall of the biliary ducts with localized stricture formation, there is biliary obstruction, followed by stasis, hypersaturation of the solids of the bile, and consequent precipitation as stones.

From the presence of specific precipitins in the blood of sheep infested with *Distoma hepaticum*, Borzone (1928) concluded that the trematodes could produce hæmolysins. This not only explains the special form of subicterus seen in patients suffering from clonorchiasis, but also the increased concentration of bile-pigments in their bile.

The excessive mucin secreted by the bile-duct epithelium in response to *Clonorchis* irritation tends to increase the viscosity of the bile and serves as a matrix, while the desquamated cells and the *Clonorchis* worms and ova serve as a nidus for the calculus. Once the stones are formed, they cause further obstruction and so a vicious circle is created.

Under normal circumstances human bile is supposed to be sterile. It is entirely possible if not probable, however, that absolute bacteriological sterility of the bile is not present constantly. Bacteria such as *Esch. coli* and anaerobic streptococci may at times, through some abrasion of the intestinal tract, gain entrance to the portal blood-stream and be excreted by the liver into the bile. These organisms cause no pathological change in the normal biliary tract. However, when there is obstruction infection may become established. With desquamation of the epithelium, the bile-duct loses its protective covering and becomes more susceptible to such infection. The end-result is cholangitis.

Once infection starts, œdema of the epithelium causes further narrowing of the lumen of the ducts and obstruction to the flow of bile. Pus cells, the slough of the epithelial lining, and the bacterial agglutinate also furnish the nidus required for stone formation. Furthermore, coliform infection changes

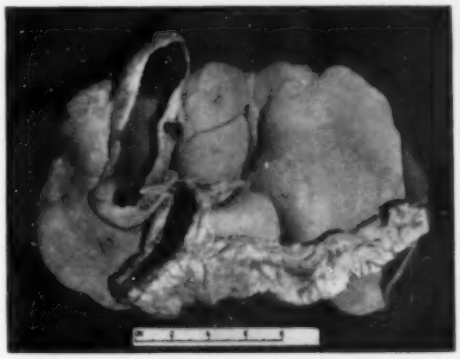

FIG. 468.—Photograph of cut surface of the liver, common bile-duct, gall-bladder, and pancreas showing large and small stones in gall-bladder and a fully packed common bile-duct. Some stones appear to assume the shape of *Clonorchis* adult worm (melon seed).

the reaction of bile from mildly acid or neutral to alkaline, which favours the precipitation of cholesterol, bilirubin, and bile-salts, contributing still another factor to stone formation.

Other factors contributing to gall-stone formation, such as disturbance of systemic cholesterol metabolism, systemic hæmolysis, and vitamin-A deficiency, have not been proved to be relevant in this disease.

Not everyone with clonorchiasis of the liver develops cholangio-hepatitis. Other contributory factors are certainly involved.

CONTRIBUTORY FACTORS

1. *Malnutrition.*—All the patients in the series belong to a poorer class and malnutrition is a definite stigma.

2. *Hypochlorhydria.*—Carter, Greene, Twiss, and Hotz (1940) found that in patients with intraductal stones and cholangitis, achylia, or hypochlorhydria was present in all cases under study. In our series, assessment of the gastric acidity has not been done as a routine. In a percentage of cases (10 per cent) in whom fractional test-meals were done, the acid curves were on the low side. This factor could be of significance in predisposing the patients to recurrent infection of the portal system.

3. *Chronic Constipation.*—A history of chronic constipation was present in 60 per cent of our cases. This may have some bearing on possible portal bacteriæmia leading to infection.

Clinically the sphincter of Oddi is usually found to be patent and devoid of stricture on exploration. Any obstructive element, then, must be due to either spasm or œdema of the sphincter as a result of one or all of the following factors:—

1. Irritation by the inflammatory process or by mechanical means such as small stones.

It has been found by Sterling (1953) that in cases of chronic calculous obstruction the ampulla of Vater has an altered reactivity threshold. The tonus of the sphincteric muscle is increased and the sphincter is irritable, responding to pressure stimuli abnormally.

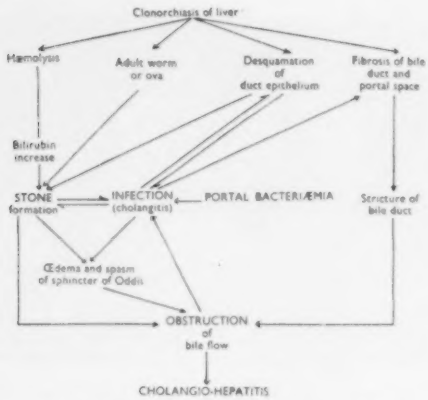

FIG. 469.—Diagram illustrating the aetiology of cholangio-hepatitis.

2. Normally, the discharge of bile through the sphincter of Oddi is dependent to some extent on contraction of the gall-bladder. The gall-bladder, having been exposed to constant infection from the infected bile, is in a state of impaired function. This is evidenced by the non-visualization of the organ in Graham's test and by the microscopical demonstration of chronic cholecystitis in all gall-bladders removed at operation. Failure of contraction of the gall-bladder may therefore contribute to some extent to stasis in the common duct and the gall-bladder, which in turn may lead to stone formation.

Once stones are formed in the common bile-duct the full picture of cholangio-hepatitis is completed. With repeated attacks of obstructive jaundice and cholangio-hepatitis, progressive liver damage results. In some, biliary cirrhosis develops (*Figs.* 469, 470).

DIFFERENTIAL DIAGNOSIS

The clinical presentation is usually typical, but other conditions have to be considered:—

1. *In the Absence of Jaundice.*—(*a*) Acute cholecystitis with or without stone; (*b*) Perforated peptic ulcer; (*c*) Acute appendicitis; (*d*) Acute pancreatitis; (*e*) Carcinoma of liver, primary or secondary; (*f*) Solitary liver abscess (cryptogenic); (*g*) Acute pyelonephritis; (*h*) Angina pectoris and other extra-abdominal conditions.

2. *In the Presence of Jaundice.*—(*a*) Infectious hepatitis; (*b*) Primary biliary cirrhosis; (*c*) Carcinoma of the lymph-nodes in porta hepatis; (*d*) Carcinoma of the head of pancreas; (*e*) Portal cirrhosis; (*f*) Carcinoma of the common bile-duct.

All these conditions have been considered in differential diagnosis and, occasionally, explored in error.

TREATMENT

As long as infestation by *Clonorchis sinensis* cannot be controlled or cured, surgeons will be faced with the burden of treating patients in whom cholangio-hepatitis develops. As each attack of this disease results in further damage to the liver parenchyma and impairment of function together with the possible and most dreaded complication of empyema

FIG. 470.—Photograph of a cut surface of the liver showing dilated intrahepatic ducts with multiple abscess cavities and intrahepatic stones.

and perforation of the gall-bladder, energetic treatment at the earliest opportunity is desirable.

Conservative treatment by antispasmodics and antibiotics together with gastro-intestinal decompression by a Ryle's tube may bring about a remission in about 15 per cent of cases. Recurrence, however, seems inevitable from clinical experience and on pathological grounds. Conservatism therefore has no place except as a pre-operative measure. Indeed, in almost any case of obstructive jaundice early surgical intervention is indicated. "It is better to look and see than to wait and see" (Bruce, 1955).

Classically, when obstructive jaundice is present, the main procedure is exploration of the biliary tree with removal of stones or biliary mud from such ducts as are accessible to instruments and irrigation. The gall-bladder is removed if diseased and the patency of the papilla is ensured. To complete the operation, the common bile-duct is closed with a T-tube for drainage and for delayed cholangiography or even irrigation of the duct should residual obstruction be present.

This treatment was employed in this condition in the University Surgical Unit up to the end of 1953. During this period, many unsatisfactory results were recorded. While the T-tube was in situ there was almost always continuous discharge of biliary mud and debris through the tube. The bacterial culture of the bile was persistently positive. Repeated cholangiograms would show the presence of intrahepatic stones and occasionally residual or newly formed stones in the common bile-duct. Daily irrigation through the T-tube with saline or other stone solvents such as ether, varidase, etc., in an attempt to clear up the infection or stones was sometimes done, with disappointing results. In some patients this procedure was carried out for a period of 3–6 months or even 12 months. Clipping of the

T-tube was often followed by obstructive symptoms such as pain, fever, and rigors. Some of the patients had to carry a T-tube for months on end, with prolonged loss of bile affecting their nutritional status.

Although the cholangiogram might finally show clearance of the bile-passage, removal of the T-tube was often followed by recurrence requiring re-exploration, whilst the prolonged indwelling T-tube contributes to the persistence of infection as a nylon stitch does to a septic wound. The hazard of stricture formation due to pressure necrosis of the duct had also to be taken into consideration.

The persistence of infection and obstruction in the biliary tract is clearly due to the presence of residual intrahepatic stones, and rational treatment ideally is to remove them. Here the real problem arises. Since most of them are peripherally situated, they are far beyond the reach of any instrument introduced through the choledochotomy wound, apart from the presence of strictures. Irrigation with saline of the biliary tree at the time of operation will help to flush out only the smaller ones. The use of fibrin and thrombin introduced through a catheter for the removal of intrahepatic stones, as suggested by Sterling (1955b), will similarly fail. One other procedure which may help to remove intrahepatic stones peripherally located is to do a partial hepatectomy, to pick out the stones, and to drain the biliary tree in retrograde fashion with hepatico-jejunostomy as suggested by Aird and Buckwalter (1955) for the pancreas. Unfortunately our patients are usually too ill for this formidable operation and the intrahepatic stones are in multiple and scattered areas.

Failing treatment of the cause, the alternative is adequate and prolonged internal drainage of the common bile-duct, so that whatever stone or debris there may be coming down from the intrahepatic source may escape into the bowel without giving rise to obstruction. Internal drainage may be provided either:—

1. By an internal fistula of adequate calibre between the common bile-duct and the intestinal tract, or

2. By relief of spasm or other obstruction in the papilla.

For the first procedure choledocho-duodenostomy and choledocho-jejunostomy seem equally efficient, and the former is much the easier to perform. It was first employed by Digby (1934), who did the operation in two stages, with preliminary cholecystostomy in the acute phase followed by end-to-side choledocho-duodenostomy 3–6 weeks later.

CHOLEDOCHO-DUODENOSTOMY

From the beginning of 1954 choledocho-duodenostomy was the treatment adopted by the Unit with certain modifications, the whole operation being done as a primary procedure in the acute stage and side-to-side anastomosis used. The operation was clearly described in detail by Stock and Tinckler (1955).

Briefly, the procedure is as follows. Pre-operatively, the patient is treated with Ryle's tube to decompress the alimentary tract. Intravenous fluid therapy is given for the correction of water and electrolyte depletion. Parenteral administration of vitamins K and C and penicillin and streptomycin or chloramphenicol are also prescribed. The patient is premedicated with morphine and atropine and anæsthetized with pentothal, curare, and gas and oxygen. Kocher's or a right trans-rectus incision is used as indicated and the common bile-duct is explored as usual. To avoid spillage of infected bile into the wound, which is usually followed by protracted wound infection (the wound infection rate was 25 per cent), skin towels or pieces of jaconet are clipped to the peritoneum instead of to the skin edges and the operation field is carefully packed off.

The opening in the common bile-duct is made as low down as possible in the supraduodenal portion of the duct. This is to make the anastomosis easier and to avoid undue rotation and angulation of the duodenum after anastomosis. The incision in the common bile-duct may be longitudinal or transverse. When the duct is dilated, a transverse cut, 1·5–2 cm. in length, is preferable, as it ensures a wide stoma at the lowest possible level. Adhesions between duct and duodenum support the anastomosis posteriorly. A small strip of the common bile-duct may be removed to provide a wider stoma instead of a slit and for biopsy.

The anastomosis is done by either interrupted or continuous inverting all-coat sutures of catgut. As the serosa of the lesser omentum is usually thickened by chronic inflammation, it can be sutured to the seromuscular coat of the duodenum as a second layer.

If the gall-bladder is found to be grossly diseased, it is removed before the anastomosis is performed. The operation is completed by a drain to Morison's pouch.

In a limited number of cases either cholecystostomy or choledochostomy with the T-tube at a higher level has been added to ensure free drainage.

Side-to-side anastomosis is preferable to end-to-side anastomosis because of its simplicity in patients with impaired liver function. End-to-side anastomosis as practised by Digby (1934) entails dissection of the common bile-duct from the portal vein, which can be extremely dangerous in the presence of chronic or acute inflammation. Damage to the blood-supply of the common bile-duct may lead to stricture formation at the stoma, as it does occasionally to the transplanted ureter. The distal stump of the common bile-duct also presents a problem. If the sphincter of Oddi is patent, it becomes a duodenal diverticulum; if obstructed, a closed abscess cavity.

Table V.—Recurrence Rates by Various Forms of Treatment of Cholangio-hepatitis

Type of Treatment	*No. of Cases*	*No. of Cases with Recurrence*	*Percentage Recurrence Rate*	
Conservative	28	23	82·1	
Choledochostomy only	14	10	71·4	
Cholecystectomy	3	2	66·6	
Cholecystectomy and choledochostomy	41	20	41·4	
Choledocho-duodenostomy	63	11	15·8	10
Choledocho-duodenostomy and cholecystectomy	78	3	3·8	
Transduodenal sphincterotomy and cholecystectomy	16	0	0	

From the beginning of 1954 to the end of 1958, 141 cases of cholangio-hepatitis were treated by

choledocho-duodenostomy and the recurrence rate brought down to 10 per cent (*Table V*).

Recurrences presented with epigastric pain, fever, and sometimes jaundice. In 5 of the cases there was abscess formation in the liver requiring surgical drainage. The others subsided after antibiotic treatment. In 2 patients there were repeated recurrences within a period of 2 years.

In all these cases radiographic examination of the abdomen showed air in the biliary tract, signifying

FIG. 471.—Radiograph of abdomen in patient 18 months after choledocho-duodenostomy, showing gas in dilated biliary tree.

patency of the anastomosis though not necessarily adequacy of the stoma (*Fig.* 471).

Lahey and Pyrtek (1950) showed that biliary fistulæ tend to close because of the low internal pressure. In this respect Digby's end-to-side choledocho-duodenostomy may be superior to the side-to-side method. In both, the motility of the duodenum may favour scar formation.

In addition to possible stenosis of the stoma, biliary stasis and stone formation in the cul-de-sac of the common bile-duct distal to the stoma may occur. This may cause œdema of the stoma, a ball-valve action giving rise to intermittent obstruction, as was actually seen in 2 cases. In one there was stenosis and in the other a large recurrent stone distal to a widely patent stoma.

The question of reflux of duodenal contents into the common bile-duct causing ascending cholangitis is debatable. It was demonstrated by Gray, Probstein, and Sachar (1943) in dog experiments that intestinal bacteria as well as pancreatic ferments can be recovered from the gall-bladder and biliary tree after choledocho-duodenostomy and choledocho-jejunostomy. But in further studies Musgrove, Grindlay, and Karlson (1952) concluded that the ill-effect if any was due to associated obstruction rather than reflux alone. This was further supported by Walters and Heim (1946). In our cases post-operative barium studies in the Trendelenburg position regularly show reflux into the common bile-duct through the stoma outlining the biliary tree. Later pictures show complete clearance of the barium from the biliary tree so long as the stoma is of adequate size. There had never been any ill-effect following this investigation so reflux *per se* is probably not the main cause of recurrence unless stricture of the stoma is also present.

Cases in which strictures were found in the large intrahepatic ducts at operation or by post-operative cholangiography suffer recurrences due to intrahepatic obstruction. The pain in these cases is mainly localized to the corresponding lobe of the liver and there is no clinical jaundice.

SPHINCTEROTOMY AND SPHINCTEROPLASTY

In order to obviate the disadvantages of choledocho-duodenostomy it seemed rational to direct attention to the lower end of the common bile-duct.

Gray, Probstein, and Sachar (1943, 1949) demonstrated the presence of diastase in the gall-bladder and evidence of chronic cholecystitis in dogs after sphincterotomy, and suggested that reflux of duodenal content might produce cholangitis after sphincterotomy. On the other hand, Archibald and Mullally (1913), Doubilet (1954), Jones and Smith (1952), and others who have extensive experience of this operation differ from this view. Miller (1956) did sphincterotomy in 8 cases with recurrent common bile-duct stones and pointed out that sphincterotomy *per se* does not lead to cholangitis. The latter, again, is caused by stenosis of the sphincterotomy wound. If this can be prevented, the results should be excellent.

Originally Doubilet and Mulholland (1948a,b) used internal sphincterotomy, but their recurrence rate was high owing either to incomplete severance of the sphincteric muscles or subsequent stenosis. Priestley, Taylor, and Roberts (1955) pointed out that, with improved surgical technique and wide-spectrum antibiotics, the duodenum can be opened with safety and the standard approach is now trans-duodenal. Doubilet (1954) has devised a special catheter to facilitate the identification and incision of the ampulla, while others employ the old-fashioned grooved director or stone forceps for this purpose.

The transduodenal route has one added advantage. The papilla and the ampulla can be inspected directly and malignancy excluded.

Jones and Smith (1952) described sphincteroplasty in which a wedge of the sphincter and duodenal wall is excised, followed by mucosa-to-mucosa anastomosis. This procedure creates as wide an opening as does choledocho-duodenostomy.

The question of cholecystectomy now needs reconsideration.

The sphincter of Oddi normally causes an increase of intraductal pressure just sufficient to fill the gall-bladder. In animal experiments Colp, Doubilet, and Gerber (1936) showed that destruction of the sphincter of Oddi leads to complete loss of the function of the gall-bladder, which becomes a flaccid diverticulum with consequent stasis, gall-stone formation, and cholecystitis. Therefore, instead of doing cholecystectomy selectively when performing sphincterotomy, the organ should be removed routinely. In

any case, even the most innocent looking gall-bladders that have been removed in this series have shown chronic cholecystitis both by cholecystography and by microscopical examination.

This whole concept has been put to use in 16 patients: in 5 sphincterotomy was done and in 11 sphincteroplasty.

The operative procedure is as follows: The patient is prepared and the abdomen is opened as for choledocho-duodenostomy. The liver, gall-bladder, common bile-duct, and pancreas are explored and assessed as usual. In order to provide better access to the common bile-duct the gall-bladder is removed as the first step of the operation. For the convenience of exploring the extrahepatic and intrahepatic ducts and later to facilitate the location of the ampulla of Vater transduodenally, the common bile-duct is opened between stay sutures in the supraduodenal portion. This choledochotomy wound is, of course, made at a higher level than that for choledocho-duodenostomy. The biliary tree is explored in the usual way. At the completion of the surgical toilet the choledochotomy region is temporarily packed off while attention is turned to the duodenum.

The hepatic flexure of the colon is turned down and the duodenum mobilized by Kocher's manœuvre. With a pair of stone forceps or Bakes dilator in the common bile-duct the site of the ampulla of Vater can be located by palpation. The duodenum is then opened between stay sutures for a length of 3 cm. just opposite to the ampulla. Two stay stitches are then inserted in the ampulla on either side of the proposed line of sphincterotomy. These, when put on traction, bring the ampullary region forwards into the duodenotomy wound and facilitate the sphincterotomy. With pressure on the stone forceps making the ampulla more prominent, the latter is incised in its anterolateral aspect, to avoid injury to the pancreatic duct which enters the ampulla usually on the posteromedial side. The incision of the ampulla is made with a sharp instrument and not diathermy current, as the latter causes necrosis and scarring. The stone forceps are then passed through the incision into the duodenum. With the blades of the forceps kept open, the incision in the ampulla and duodenal wall is lengthened. This is followed by approximation of the duodenal mucosa to the common bile-duct mucosa with interrupted suture of atraumatic No. 00 catgut. The total length of the incision through the ampulla is 1·5 cm., giving an ample opening to the lower end of the common bile-duct.

If sphincteroplasty is to be done, a small wedge of the common bile-duct, duodenal wall, and sphincteric muscle is excised from the lateral edge of the incision. This results in the formation of a wide, trough-like stoma.

The duodenotomy is then closed transversely and the choledochotomy closed over a T-tube, later used for delayed cholangiography and measurement of intracholedochal pressure, after which it is clipped at first intermittently and later continuously. It is removed after it has been clipped continuously for 48 hours, the patient not complaining of discomfort, usually around the fourteenth post-operative day. It is pointed out by Jones and Smith (1952) that should a sphincteroplasty have been done, prolonged drainage with a long-armed T-tube is not necessary, as scarring is minimal after mucosa-to-mucosa approximation. The wide excision of duodenal musculature also minimizes the constricting action of the duodenal wall on the lower end of the duct. The operation is completed by closing the abdominal wound in layers with a Penrose drain to Morison's pouch.

Post-operatively, the Ryle's tube is aspirated hourly, fluid and electrolytes replaced, and antibiotics continued to prevent infection from spillage. Oral fluid in small quantity is given after 48 hours provided the amount of aspiration is minimal. Bland fluid diet can usually be started by the third post-operative day.

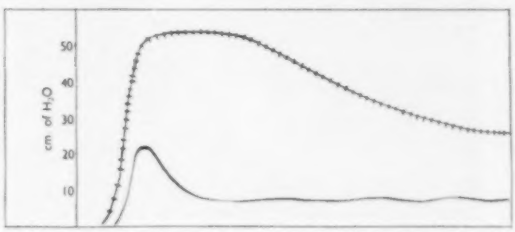

FIG. 472.—Pre- and post-sphincterotomy choledochometrograph through a T-tube.

The convalescence of all the patients has been smooth. Delayed cholangiograms reveal rapid emptying of the dye into the duodenum. Barium-meal studies in Trendelenburg position show reflux into and rapid clearance from the biliary tree of the barium. Manometric study of the intracholedochal pressure reveals a low tracing stabilizing regularly at or below 8 cm. of water, confirming the destruction of function of the sphincter of Oddi (*Fig.* 472). All these patients (except 1) have been free from symptoms since operation for periods ranging from 3 to 18 months (*see Table V*). One patient died two weeks after operation of hepatic failure. Post-mortem examination showed a large, malignant cholangioma in the right lobe, with multiple secondary nodules in the parenchyma of both lobes of the liver.

Complications specifically following transduodenal sphincterotomy or sphincteroplasty are few, as reported by various authors:—

1. Duodenal leak with all its sequelæ, such as subphrenic abscess, peritonitis, and duodenal fistula, is rare. This can be prevented by meticulous closure of the duodenotomy and gastric decompression by aspiration in the early post-operative period. This complication was encountered in one case.

2. Duodenal obstruction may occur, but usually transiently. This may be due to early post-operative œdema in the second part of the duodenum and will usually subside in a matter of 4–5 days. Undue narrowing of the duodenum should never occur if the duodenotomy wound is closed transversely.

3. Post-operative acute pancreatitis after division of the sphincter of Oddi has been reported by Blatherwick and Pattison (1954), presumably due to œdematous obstruction of the pancreatic duct orifice or actual severance of the duct. This very rare

complication should be obviated by placing the incision of the papilla on its anterolateral aspect and by gentle handling of the tissues.

4. Post-operative stenosis of the ampulla of Vater after sphincterotomy has been a relatively common complication in the past. It can be avoided by meticulous approximation of the layers of mucosa.

FIG. 473.—Retrograde cholangiogram done through a cholecystostomy tube of a case showing stones in common bile-duct and ampulla of Vater. The whole biliary tree is markedly dilated, with stricture formation in the intrahepatic ducts.

FIG. 474.—Post-operative cholangiogram of same case as *Fig.* 473 after transduodenal sphincteroplasty.

Prolonged drainage with long-armed T-tube as advocated by Lahey and Pyrtek (1950) and Maingot (1956) may be instituted in case of doubt. In sphincteroplasty this complication is a rarity.

5. The question of biliary dyskinesia after sphincterotomy has not been raised. In our series dyspepsia after a meal has not been complained of in follow-up studies. It is probably more theoretical than real.

With the exception of a transient duodenal leak in one of the patients in whom the primary choledochostomy wound had been done in a relatively low position in the common bile-duct, none of these complications has been encountered in our series.

The problem of residual intrahepatic mud and stones after sphincterotomy or sphincteroplasty or choledocho-duodenostomy still requires attention. Cholagogues and choloretics given post-operatively for varying periods are under trial on the same principle as that followed when forced fluids and acid phosphate are employed for the control of urinary calculi. A new product by C. D. Searle & Co. called 'Zanchol' is a brand of florantyrone possessing both chologogue and choleretic actions, as proved by McGowan (1956). This has been given for a period of 3–6 weeks after choledocho-duodenostomy or sphincterotomy and the result as regards the change of colour, increase of volume, and decrease of sediments and viscosity of the bile draining from the T-tube has been up to expectations. Duodenal intubation of these patients in later follow-up studies has shown a satisfactory decrease in the biliary mud concentration in the bile.

The early results of sphincterotomy and sphincteroplasty (*Figs.* 473, 474, *Table V*) in the treatment of recurrent cholangio-hepatitis have been encouraging and in the long term should, theoretically at least, be comparable with those reported in treating relapsing pancreatitis.

SUMMARY

1. The clinical and pathological features of recurrent cholangio-hepatitis occurring in the Chinese community in Hong Kong are described.

2. The aetiological factor—clonorchiasis; the predisposing factors—malnutrition and hypochlorhydria; and the precipitating factors—intrahepatic stone formation, infection, and spasm of the sphincter of Oddi—are discussed.

3. Experience in the management of this condition by external drainage in the form of prolonged T-tube drainage and by internal drainage in the form of choledocho-duodenostomy is described and the results assessed.

4. A new approach to the problem by means of extended sphincterotomy and cholecystectomy with the post-operative administration of cholagogues and choleretics is described and the rationale and results are discussed.

Acknowledgements.—I wish to express my gratitude to Professor F. E. Stock, Professor of Surgery, University of Hong Kong, for constant guidance and for his kind permission to use the clinical material. Appreciation for the preparation of the microscopical slides by Mr. R. B. Maneely, Senior Lecturer in Anatomy, University of Hong Kong; and for the permission to copy the radiographic pictures by Dr. H. C. Ho, Senior Radiological Specialist, Queen Mary Hospital, is also expressed.

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CONSERVATIVE SURGERY IN RENAL TUBERCULOSIS

INCLUDING RENAL CAVERNOTOMY*

BY HOWARD G. HANLEY

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IT is now possible to kill the tubercle bacillus with suitable drugs provided that the dosage is adequate, the organism is sensitive, and the patient actually takes the drugs prescribed for a suitably long period of time. Genito-urinary tuberculosis can therefore be 'cured' by such drug therapy, provided that there is no obstruction to urinary drainage and that the blood-supply to the lesion is adequate.

All tuberculous lesions heal by a mechanism of protective fibrosis, and it is this very healing fibrosis which tends to obstruct the free flow of urine and also creates avascular areas filled with caseating debris. Unfortunately, simple urinary obstruction will destroy renal tissue just as surely as the tuberculous process, while caseating areas, being inaccessible to the drugs, may persist as latent foci of infection, always ready to break down when the host resistance is lowered.

The present-day surgery of genito-urinary tuberculosis is therefore directed to the maintenance or provision of urinary drainage and the evacuation of large areas of avascular caseation.

The three main danger sites for fibrosis and urinary obstruction are (1) the lower end of the ureter, (2) the pelvi-ureteric junction, and (3) the neck of a calix.

LOWER URETERIC OBSTRUCTION

Strictures at the lower end of the ureter are very satisfactorily dealt with by re-implantation or by some other form of diversion (Hanley, 1957, 1958; Puigvert, 1951).

OBSTRUCTION AT THE PELVI-URETERIC JUNCTION

Obstruction at this site produces a straightforward pyonephrosis and is the chief indication for nephrectomy in renal tuberculosis. Awareness of this danger should make it possible to detect such a progressive lesion at an earlier stage than heretofore, and we have now performed three successful plastic operations for obstruction at the pelvi-ureteric junction.

The first patient had a nephrostomy drainage from a solitary kidney which had been free from tubercle bacilli for over a year. A Davis intubated ureterostomy was performed, the splint being left in situ for six weeks. The newly formed pelvi-ureteric junction was examined carefully under the X-ray image intensifier before the nephrostomy tube was finally removed. This patient is still alive and well two years after the closure of the nephrostomy. The pyelogram is still bizarre, but the kidney excretes well, and the urine is sterile.

The second patient, with only a minimal lesion on the right side, developed a complete obstruction of the left pelvi-ureteric junction over a period of six months. Three attempts to pass a catheter into the pelvis failed and finally the kidney was explored with a view to nephrectomy. The pelvis was grossly distended with hazy urine containing living tubercle bacilli, but the parenchyma was reasonably well preserved. A Davis intubation was performed, leaving the splint in situ for six weeks and the nephrostomy tube for two months. This operation

* Based upon a paper and ciné-pyelography film presented to the Association of Surgeons of Great Britain and Ireland in London, April, 1959.

has been an unqualified success for nearly eighteen months.

The third patient was operated upon six months ago, and it may well be too early to assess the results. This was not a technically pleasing operation; the splint may not have been left in situ long enough (4 weeks) and the nephrostomy drainage did not close for three weeks after the tube was removed. However, the patient is symptomless, the urine is sterile, and the pyelogram shows a fair excretion of medium.

Selection of Cases for Pelvi-ureteric Junction Surgery.—When confronted for the first time with a closed pelvi-ureteric junction it is not possible to say whether the condition is old or recent, transitory or permanent, and repeated radiological examinations will be necessary before coming to any decision. Even then the number of cases suitable for plastic surgery of this nature will obviously be small, and will mostly be confined to those patients where the obstruction was not complete when first seen, but where it has been observed developing or progressing during drug treatment. In fact, it is a wise dictum to avoid any surgery until the patient has been reviewed at least twice during the first three months of drug therapy, and then, even on the appointed day, to be prepared to wait and think again. A ureteric catheter which has failed to pass on two or more occasions may finally do so with ease as the œdema subsides. Conservative surgery of this nature can of course—like anything else—be carried too far, and the old cliché that every case must be considered on its merits cannot be repeated too often.

The age of the patient, the psychological attitude to prolonged drug therapy and probably repeated surgery, quite apart from the state of the opposite kidney, have all to be considered. However, our results so far have been sufficiently encouraging to warrant further attempts at plastic surgery of the junction when suitable cases present themselves.

OBSTRUCTION AT THE NECK OF A CALIX

While obstruction at the pelvi-ureteric junction will destroy the whole kidney, obstruction of a calicine neck will only destroy a renal segment and is therefore less serious. However, closure of the neck leads to a pyocalix which becomes avascular and is not accessible to the anti-tuberculous drugs. Such a lesion does not respond well to conservative treatment and is always a latent focus of disease. Unfortunately, the moment the calix becomes closed the urine may become free from tubercle bacilli and this may produce a false sense of security. The sudden re-appearance of tubercle bacilli in the urine in spite of adequate drug therapy should always make one search for a hidden cavity which has re-opened.

On general principles, closed avascular caseating areas in the kidney should be removed, or drained surgically. The choice of how this should be done is greatly simplified by a knowledge of what is happening in the calices in question.

The Mechanical and Radiological Changes.—The earliest and the commonest radiological evidence of a tuberculous renal lesion is a vague irregularity of the calicine outline, due either to œdema or erosion of the lining membrane. Very soon the calix may appear to be 'clubbed' or rounded while the neck is narrowed and elongated, but at this early stage it is not possible to tell whether the clubbing is transitory due to œdema, or permanent and due to erosion of the papilla and mucosa. In other words, any single set of excretion pyelogram films will not tell us whether the lesion is progressing, quiescent, or healing. This can only be ascertained by repeated radiological study, and if the first pyelogram shows any signs of obstruction at the three danger points, it must be repeated in about two months' time. (It must be emphasized that such follow-up studies should be made with a limited number of X-ray exposures, directed chiefly to the areas under suspicion. In our own cases the area of body X-ray exposure is limited to a square of about 5 in. which is accurately localized with the X-ray intensifier.)

It has been our experience on many occasions that although all of the major calices may appear to be radiologically 'clubbed' at the first examination, a repeat X-ray after two or three months' intensive drug therapy may show that clubbing only remains in perhaps one calix and that the others have returned to normal (Hanley, 1957).

If this 'clubbing' appearance were always due to erosion of the papilla it could never return to normal, since a destroyed papilla cannot grow again. Therefore it must be possible to reproduce the radiological appearances called 'clubbing' by more than one mechanism.

Transitory Caliceal Clubbing.—The extreme mobility of the normal calix is not generally appreciated because we are only accustomed to see a shadow outline on a still radiograph, but a fluoroscopy study reveals the fact that the shape and size vary considerably, while the movement patterns, though extensive, may occur abruptly and may have a very short cycle. In many normal kidneys a contraction of the renal pelvis tends to force urine, not only into the upper ureter, but also back into the calices (chiefly the lower one). For one fleeting moment such a calix is over-distended and rounded, in fact, typically 'clubbed'. Transitory 'clubbing' is therefore relatively common and can be produced relatively easily in some patients. This phenomenon can be explained by a consideration of the simplified anatomy and physiology of the calix (*Fig.* 475).

When fluid is contained under pressure it tends to assume the shape of a sphere. Therefore, if the pressure in a calix rises for any reason at all (blockage of the neck, obstruction at the pelvi-ureteric junction, or merely reflux), the extremely loosely supported lining membrane will blow out into a sphere shape, anchored only at the tip of the papilla, and less rigidly, at the neck of the calix (*Fig.* 476 A). This condition is obviously reversible the moment the pressure is relieved and is ordinarily part of the normal caliceal movement pattern.

A similar radiological appearance can also be produced when the angles of the calices are obliterated by inflammatory œdema (*Fig.* 476 B), and will be accentuated if there is also œdema round the calicine neck. This accounts for the 'clubbing' seen on occasion during acute pyelonephritis in young

women, and certainly explains the transitory clubbing seen in renal tuberculosis. Unless the œdema is followed by fibrosis or ulceration a return to a normal radiological outline is possible and probable.

True clubbing is the result of erosion of the papilla and the mucosa and is quite irreversible (*Fig.* 476 C).

It is obviously not possible to detect which of these factors is causing clubbing if only one set of still radiographs is examined, and it is certainly not possible to judge whether the condition is transitory or permanent during one examination.

Our special consideration at the moment is the detection of permanent obstruction at the neck of the calix, for this I believe is the only indication for surgical interference.

The Closed-off Cavity.—All seriously 'clubbed' calices or areas of cavitation must be kept under regular observation for fear that they become closed off from the main collecting system. This is indicated by the radiological disappearance of the cavity shadow, and is much easier to interpret if we have previous films for comparison.

However, it is not always possible to tell whether a calix or cavity is shut off or merely filled with caseating material. If a cavity shows vaguely in excretion pyelography, but cannot be filled on retrograde examination, an obstruction is likely. If the cavity is only outlined by retrograde filling, and then only vaguely, it is probably full of caseous material (*Fig.* 477 A, B).

It is our experience that the radiological appearances of these cavities vary considerably during conservative treatment, and that the majority of them, given time, will drain out their caseous material and will subsequently heal (*Fig.* 478).

Provided that the urine remains sterile and the cavity has free communication with the major calicine system, we are not unduly concerned with the bizarre radiographic outline and are prepared to continue with conservative drug treatment. We now believe that a bizarre outline is not an indication for surgery, and we have not performed a partial nephrectomy for such a lesion for over three years. Very careful follow-up records of these cases continue to encourage us in this belief.

A serious problem arises when a closed-off cavity does not re-open. It tends to grow larger and may eventually contain 40–50 ml. of pus under tension. Its presence can only be assumed by a careful study of good quality radiographs, when a comparison of the renal outline and the pelvic shadow will reveal an area devoid of any collecting system (*Fig.* 479).

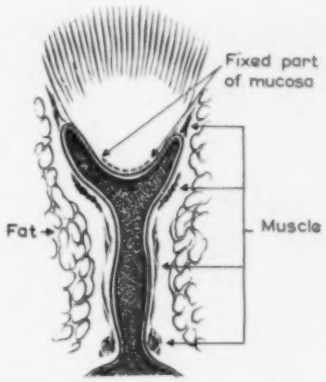


FIG. 475.—The extreme mobility of a calix is due to the fact that the only fixed point of its lining membrane is at the tip of the papilla. The rest of the structure, surrounded by well-defined muscle-bundles, lies in a soft fatty bed which allows considerable alteration in size and shape.

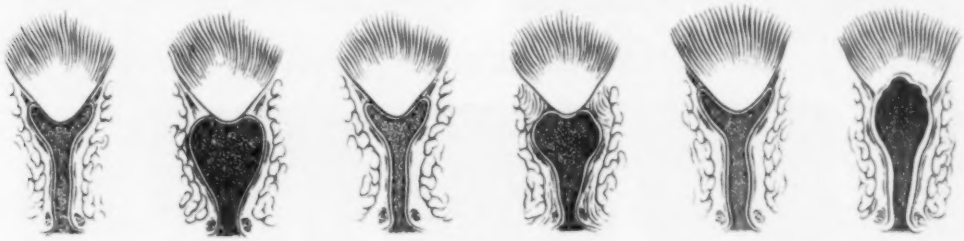


FIG. 476.—A, Because the lining membrane of the calix is only fixed at the tip of the calix where the tubules emerge, any increase of intracaliceal pressure will tend to blow out the calix into the shape of a sphere, thus obliterating the angles and producing the radiological appearance of 'clubbing'. This returns to normal when the pressure is relieved. B, The angles can be obliterated by inflammatory œdema and this will also give the appearance of 'clubbing'. If the œdema includes the calicine neck, the pressure may be raised, thus adding to the distended spherical appearance of the calix. Provided that the œdema is not followed by ulceration or fibrosis this type of 'clubbing' will return to normal. C, Erosion of the papilla will cause true 'clubbing', and is irreversible. The fluffy appearance of a tuberculous calix is due to erosion of the mucosa, but when healing and re-epithelialization occurs the outline may become smooth again.

A cavernostomy or speliotostomy is by no means a new operation (Chiaudano, 1958; Staehler, 1954). However, the principle of evacuation of pus without subsequent drainage, that is to say, a *cavernotomy* as opposed to a *cavernostomy*, has been made safe by the introduction of the anti-tuberculous drugs, and it is now a renal cavernotomy which we are performing as the operation of choice for tuberculous cavities.

RENAL CAVERNOTOMY

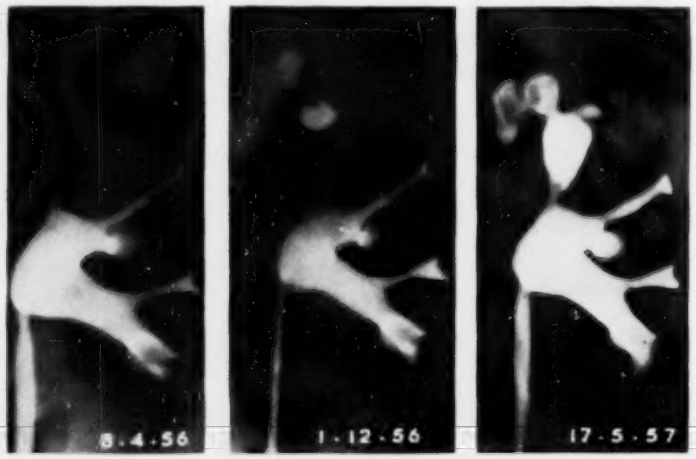
Certain fundamental principles should be observed. Prolonged intensive drug therapy will already have been administered, during which time repeated radiographic studies will have confirmed the fact that the cavity or cavities are indeed completely closed. Failure to observe this last point may lead to a troublesome post-operative urinary fistula, quite apart from the fact that, if the cavity had a free communication with the pelvis, a little more time and patience might have shown the operation to be quite unnecessary. There is seldom any urgency associated with this operation.

Operative Technique.—The kidney is exposed through the bed of the lowest prominent rib. When the surrounding fat has been cleaned away from the capsule the abscess is generally visible and palpable.

As a preliminary step it is advisable to aspirate all the fluid contents through a large-bore needle. This has the effect of collapsing the abscess roof, thus revealing the limits of its walls. The centre of the roof, which will be relatively avascular, is now

A B

FIG. 477.—A, Excretion pyelogram showing cavity in relation to the lower calicine group. B, Retrograde pyelogram performed a few days after film A. The lowest group cannot be filled, indicating a very tight calicine neck.



A B C

FIG. 478.—A, Absence of upper calicine group, indicating either blockage of the neck or obliteration of the cavity space by caseous material. B, Six months later; the upper calicine group has started to drain away into the pelvis. C, Five months later still there is free drainage of the whole area. The urine is sterile and the lesion is healing. This calicine group has remained unaltered for over two years. The urine is sterile and the lesion is presumed to be 'quiescent'.

grasped with toothed dissecting forceps and is cut open with scissors. A piece should be removed large enough to enable the cavity to be cleaned out gently with small dry swabs until all the whitish slough has been removed down to healthy red granulation tissue (*Fig.* 480).

Gentleness is essential during this manœuvre; too vigorous rubbing of the walls of the cavity will result in vascular oozing which may be difficult to control. Care must be taken when extending the resection of the cavity roof. The dome becomes progressively vascular towards the periphery and resection should be stopped short of continuous bleeding. This will mean that there is quite a marked overhanging lip all the way round.

No attempt should be made to 'saucerize' the cavity, since the overhanging rim is essential for

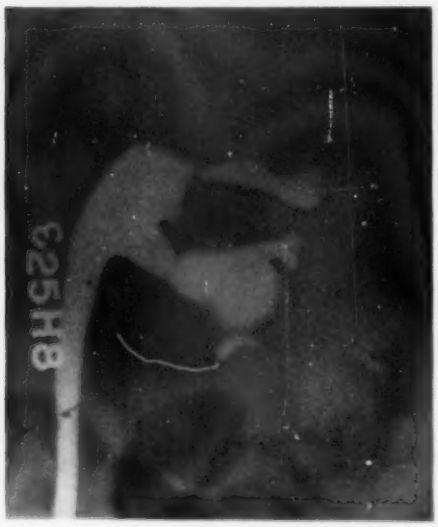


FIG. 479.—Space-filling lesion due to large closed abscess cavity in upper pole of left kidney; 40 ml. of thick pus was evacuated during the cavernotomy.

hæmostasis. Any bleeding edges can be oversewn with 000 catgut, but this is very difficult if the thin rim has been removed (*Fig.* 480, *inset*). The walls of the cavity and its rim must be absolutely dry at the completion of the operation. The original obliterated calicine neck can generally be seen as a blind dimple at the bottom of the cavity, but one's natural inclination to explore this with a probe should be curbed.

Nothing now remains but to replace the kidney in its bed and complete the closure of the incision. No drainage of any sort is employed. It is difficult to understand the rationale of irrigating with antibiotic solutions. The serum of the patient who is receiving adequate doses of anti-tuberculous drugs will be far more toxic to the tubercle bacillus than anything we can inject down a tube (and will be sterile!).

The maximum amount of pus so far evacuated from one cavity has been 70 ml., but over 100 ml. has been removed from three separate cavities in the same kidney, while 160 ml. has been removed from five cavities in the two kidneys of the same patient (*Fig.* 481). Tubercle bacilli have been cultured from the caseous material lining the cavities in over half of the cases so examined.

Only 1 sinus has developed following 33 operations in 28 patients. One woman developed a small 'stitch abscess' in her wound several months after

FIG. 480.—Renal cavernotomy. The abscess has been aspirated through a wide-bore needle. As the roof collapses the limits of the cavity are clearly defined. The centre of the roof, which is relatively avascular, is resected, care being taken to preserve an overhanging edge which can be oversewn for hæmostatic purposes where necessary (*inset*). The remaining caseous material is gently removed with dry gauze swabs. Undue roughness at this stage will result in troublesome oozing of blood from the granulating walls.

completing her sanatorium treatment. It did not drain profusely—in fact on some days it was almost dry—but it eventually became obvious that the sinus extended down to the kidney. No urine has escaped at any time. The track has only recently been resected.

Apart from this one sinus all of the patients have continued to progress most satisfactorily. Sixteen of them have completed the post-sanatorium ambulatory course of drugs and the urine continues to remain free from tubercle bacilli. No mortality or serious morbidity has been encountered.

In our hands, at least, a cavernotomy is a simpler and much safer procedure than a partial nephrectomy and appears to be equally effective. It is more conservative of renal tissue and can be employed

with confidence in cases which are too extensive for partial nephrectomy. For example, it would be interesting to speculate how much renal tissue would remain after a partial resection of the upper, middle, and lower poles of the left kidney shown in *Fig.* 481.

FIG. 481.—Composite diagram. The renal outlines and the solid black areas are tracings from retrograde pyelogram films. The shaded areas indicate the situation of the pus-containing cavities found at operation. The left mid-zone cavity, though broad in outline, was shallow, contained only 10 ml. of pus, and lay just under the surface of the posterior aspect of the kidney. A total of 160 ml. of pus was evacuated from these five cavities.

SUMMARY

Renal tuberculosis can be controlled by drug therapy provided that there is no obstruction to urinary drainage, and that the blood-supply to the lesion is adequate.

Unfortunately, tuberculosis heals by fibrosis, so that healing and urinary obstruction can occur simultaneously. An ulcerating lesion which is not free to drain will be surrounded by fibrous tissue and will become caseous. Such a lesion is avascular and is not accessible to the blood-borne drugs. The chief indications for surgery are, therefore, the maintenance or promotion of urinary drainage and the removal of caseous material.

Conservative surgery of the pelvi-ureteric junction is discussed and 3 cases of Davis-intubated ureterostomy are recorded.

Obstruction of the neck of a calix leads to a pyocalix. Under adequate drug therapy a majority of these calices will re-open and drain, resulting in a distorted but healed and freely draining cavity. No surgery is indicated.

When the obstruction is permanent and a large cold abscess develops in the parenchyma, this is avascular and does not respond satisfactorily to drug therapy. Consistently good results have followed the performance of a cavernotomy in such cases.

Thirty-three cavernotomy operations are recorded without mortality. Five patients had bilateral operations, one patient having five cavities drained.

I wish to thank Miss Freda Wadsworth for her excellent illustrations.

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METASTASIS TO THE BLADDER FROM CARCINOMA OF THE KIDNEY

BY RICHARD E. SHAW, COVENTRY

CASE REPORT*

A man aged 68 years attended the Coventry and Warwickshire Hospital in October, 1957, with a history of having passed blood in his urine three times during the previous fortnight. He also complained of some frequency, having to rise three times during the night to pass urine. There had been no pain. Physical examination was negative, except for evidence of early benign prostatic enlargement and of hypertension. Blood-pressure was 190/120.

ON EXAMINATION.—

At cystoscopy a smooth, rounded tumour was seen hanging by a stalk from the fundus of the bladder.

An intravenous pyelogram (*Fig.* 482) showed no evidence of function in the left kidney. The right kidney appeared normal.

A left retrograde pyelogram (*Fig.* 483) showed a little deformity of the left upper calix, but no gross abnormality was seen.

The urine contained many red cells, and streptococci and staphylococci were cultured. The blood-urea estimation and blood-count were normal.

FIRST OPERATION.—On Nov. 20, 1957, the bladder was explored and an ovoid tumour (*Fig.* 484) 2½ × 1 cm. was removed from the fundus by ligating and dividing its pedicle. Histologically, the tumour (*Figs.* 485, 486) showed the characteristic appearances of a clear-cell carcinoma of the kidney.

SECOND OPERATION.—After recovery from the first operation, a left nephrectomy was performed. The renal vein was clear of growth at the site of division of the renal pedicle.

Dr. E. N. Trounson reported on the specimen as follows: "A variegated yellow and hæmorrhagic tumour 6 cm. in diameter is situated at the upper pole; several other nodules up to 1 cm. in diameter occupy chiefly the medullary pyramids or the pelvic fat at varying distances from the main growth; one is situated in the cortex at the opposite pole. There is no naked-eye involvement of the main renal vein. Histology—the large tumour is a typical clear-celled renal adenocarcinoma. The other nodules appear to be retrograde venous metastases." (*Fig.* 487.)

PROGRESS.—The patient underwent a course of post-operative radiotherapy to the left loin. He never quite recovered his previous health and a year after the operations showed signs of metastases in the right clavicle and scapula; thereafter his condition rapidly declined.

* This case was presented to the Urological Section of the Royal Society of Medicine on March 19, 1959.

FIG. 482.—Intravenous pyelogram showing absence of function on the left side.

FIG. 483.—Left retrograde pyelogram. There is a little deformity of the upper calix.

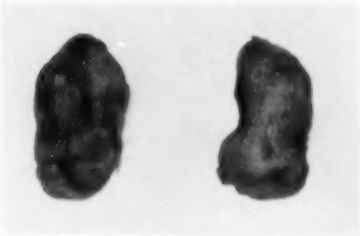

FIG. 484.—The tumour removed from the bladder.

DISCUSSION

In cases of papillary tumours of the renal pelvis, additional deposits of tumour tissue are frequently present in the corresponding ureter and in the bladder. On the other hand, metastases in the ureter and bladder are extremely rare in cases of renal carcinoma (hypernephroma). Abeshouse (1956) reviewed all the recorded cases of clear-cell carcinoma of the kidney metastasizing to other parts of the genito-urinary tract. He found 61 examples; 15 with deposits in the ureter, 8 in the bladder, 3 in the penis, and 5 in the testes. He added 2 cases of his own with bladder metastases. Including the case reported in this paper, there appear to be 10 authentic cases of renal carcinoma associated with metastases in the bladder. These are enumerated in *Table I*.

The main point of interest in these cases is the route of spread from kidney to bladder. It is tempting to regard the metastases as arising by implantation, tumour cells in the urine being grafted on mucosa lower down in the urinary tract. This is the mechanism assumed by MacAlpine (1948) in his well-known paper on spread of renal carcinoma to ureter and bladder. It is unlikely to be true. This mode of spread is now regarded as unlikely even in the papillary tumour of the renal pelvis, previously regarded as the classic example of implantation, and most workers now regard the deposits in the ureter and bladder as independent tumours produced by carcinogenic agents in the urine. A much more likely mode of spread is by retrograde venous embolism. The left renal vein, unlike its fellow, has numerous connexions with the suprarenal, lumbar, and phrenic veins, and also receives the testicular or ovarian veins. These communications put the venous system of the left kidney into direct communication with the pelvic, parietal, phrenic, vertebral, and gonadal systems. The tendency of renal carcinomata to invade the renal vein is well known and it is easy to visualize, how, in conditions of raised intra-abdominal pressure, as in coughing or sneezing, tumour emboli may become dislodged and swept into these organs. Powerful support for this theory is found in the high incidence of the left kidney as the site of the primary growth in

Table I.—REPORTED CASES OF METASTASES IN THE BLADDER FROM RENAL CARCINOMA

Author		*Side of Primary Tumour*
Seizo-Suzuki (1909)		Left
Szymonowicz (1932)		Left
Cibert and Perrin (1938)		Right
Rupel and Sutton (1950)		Left
Scott (1952)		Not mentioned
Heslin, Milner, and Garlick (1955)	*Case* 1	Left
	Case 2	Right
Abeshouse (1956)	*Case* 1	Left
	Case 2	Left
Shaw (1961)		Left
	Totals:	Left 7
		Right 2
		Unknown 1

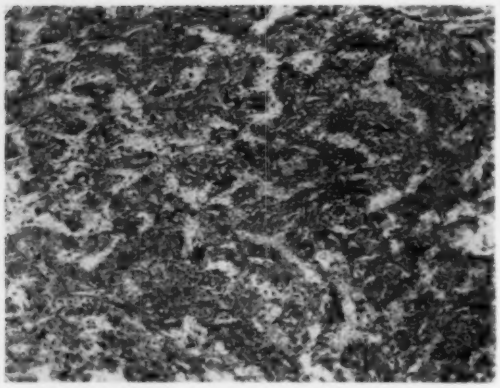

FIG. 485.—Histological appearance of the bladder tumour (low-power). It is a typical clear-cell carcinoma. (× 60.)

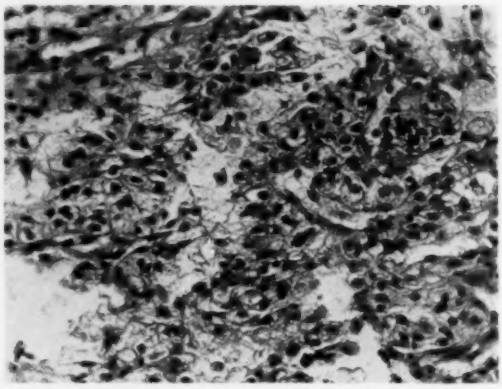

FIG. 486.—Histological appearances of the bladder tumour (high-power). (× 225.)

cases with metastasis to the pelvic organs. From *Table I* it will be seen that out of 9 cases in which the side was mentioned, the left was responsible in 7. Similar figures are given by Abeshouse for the predominance of the left side in metastases to other pelvic organs—8 out of 12 cases of ureteric metastases, 3 out of 3 penile metastases, 4 out of 5 testicular metastases, and 20 out of 25 vaginal metastases. Further support is obtained in the present case by the unusual deposits of tumour tissue which may be seen throughout the kidney. It seems likely, as suggested by Dr. Trounson, that spread by venous embolism was taking place within the kidney itself. Blockage of the smaller radicles of the renal vein by the emboli may also account for the absence of any function in the kidney on intravenous pyelography, despite the absence of growth in the main renal vein.

Willis (1934) drew attention to cases of carcinoma of the kidney presenting with metastases in the vagina or vulva, which he attributed to retrograde embolism down the left ovarian vein after occlusion of the renal vein by tumour tissue. He pointed out that in these cases the primary lesion is nearly always on the left side. Abeshouse suggests that a similar mechanism can explain the presence of metastases in the bladder, ureter, penis, urethra, and testis. It should be mentioned that Willis is sceptical of retrograde venous embolism taking place in the absence of mechanical block to one of the main veins, and in the case reported in this paper the trunk of the renal vein was free of growth.

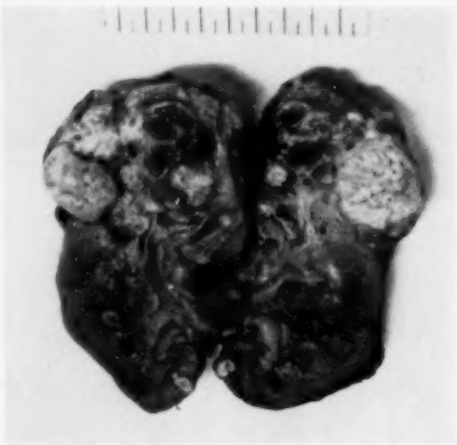

FIG. 487.—The left kidney after removal showing the main tumour mass in the upper pole and further nodules in the rest of the organ.

SUMMARY

1. A case is described of carcinoma of the left kidney presenting with symptoms from a metastasis in the bladder.

2. It is suggested that the mechanism of spread from kidney to bladder was by retrograde venous embolism.

I wish to express my thanks to Dr. J. E. Glasgow for the radiological examinations, to Dr. E. N. Trounson for the pathological reports, and to Mr. P. H. Partridge for the photographs of the specimens.

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A CASE OF HÆMORRHAGE FROM VARICES IN THE SMALL INTESTINE DUE TO PORTAL HYPERTENSION

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THE case presented is one in which bleeding occurred from varices in the small intestine in a patient known to have had portal hypertension and peptic ulceration. The details are given below in chronological order, but apart from the patient's historical account much of this was unknown before operation.

CASE REPORT

The patient was admitted to the Professorial Surgical Unit at the Manchester Royal Infirmary from another hospital on Dec. 20, 1958. He was 58 years of age. He first had gastro-intestinal hæmorrhage in 1936 at the age of 28 years. Before this he could remember no significant illness. The first attack had started with faintness, a vomit of half a pint of blood, and the passage of tarry stools for the following four or five days. There had been no abdominal pain. He had further similar episodes in 1939, in May and November, 1940, and in April and November, 1945. He had several barium meals, but nothing abnormal was noted until November, 1945, when œsophageal varices were demonstrated. A diagnosis of splenic anæmia with leucopenia was made and a splenectomy was performed. At this operation the spleen was grossly enlarged and the liver was described as "slightly enlarged, firm and with a somewhat irregular nodular edge". The liver function tests at this time were within normal limits.

The patient had no further bleeding until December, 1952, when he had an attack of melæna, and about the same time began to complain of epigastric pain with characteristics suggesting a peptic ulcer. The pain was present intermittently after this date. A gastric ulcer was demonstrated by barium meal in 1956, but was not seen a year later, and œsophageal varices were also seen on both occasions. He had another attack of melæna in 1956, and nothing further until the attack during which he was admitted in December, 1958.

This episode started on Dec. 16, 1958, when he felt dizzy, and on defæcation passed a large dark red liquid stool. He had five further melænas until his admission to another hospital on Dec. 19, where he was transfused with three bottles of blood. On arrival in Manchester Royal Infirmary on Dec. 20, he was obviously pale. There was a left paramedian scar which in its upper part had herniated. In the lower part of the scar near the umbilicus several large varices were visible in the abdominal wall. The liver was not palpable, there were no spider nævi, and the palms of his hands were a normal colour. His mental state was normal and there was no flapping tremor. His blood-pressure was 150/70 and pulse-rate 96/minute.

Shortly after admission he passed a dark red fluid motion of 800 ml. and later a further 100 ml. and became rather shocked. A Blakemore-Sengstaken tube was passed with the intention of occluding his œsophageal varices, but during this manipulation he vomited about 200 ml. of gastric content which did not contain blood. The balloons of the Blakemore-Sengstaken tube were therefore not inflated. (Later gastric aspirations were not blood-stained.) Five bottles of blood were given in the next twelve hours. Prothrombin activity was estimated and found to be 100 per cent of average normal.

It was thought at this point that the patient had portal hypertension in view of his previous history and the visible varices on the abdominal wall, but since the gastric contents did not contain blood shortly after an episode of bleeding, he was presumed to have bled from a duodenal ulcer. It was not known whether he had cirrhotic changes producing portal hypertension, but he was given neomycin 1 g. 4-hourly down the gastric tube to produce intestinal sterility as prophylaxis against hepatic coma.

He had no melæna on the following day and his clinical state improved, but at 5 a.m. on Dec. 22 he complained again of dizziness, passed more dark red fluid motions, and became moderately shocked. His blood-pressure fell to 95/50 and his pulse-rate rose to 120/minute. He was transfused with a further two bottles of blood and laparotomy was undertaken.

Incision was made through the upper part of the paramedian scar, but was diverted to the midline in the lower part to avoid the varices in the abdominal wall previously mentioned. There were a few vascular adhesions in the upper part of the abdominal cavity. A loop of small intestine was adherent to the lower scar and associated with the varices. The liver was moderately cirrhotic. The stomach and duodenum appeared normal on palpation and inspection. An incision was made into the stomach and duodenum through the pylorus. Clear bile was seen welling up in the duodenum and the stomach was normal. The small intestine was inspected and it was seen that the blood in it did not extend much higher than the ileal loop which was adherent to the scar. In the mesentery there was an enormously dilated vein about 1 cm. in diameter running to the apex of the loop. The gut was opened to display two submucosal varices, one of which was 1 cm. across, and which had on its dome a greenish ulcerated area of 3 mm. diameter. This was not then bleeding, but it bled furiously after pressure had displaced the plugging clot. The loop was detached from the abdominal wall, the segment containing varices excised, and repaired by end-to-end anastomosis. In detaching it several large veins passing from the loop to the wall were cut through. The area of adhesions was about 3 sq. cm. The pyloric wound was repaired. A liver biopsy was not taken. Since the incision was through a previously herniated area and repair was not contemplated, the abdominal wall was sewn up with mono filament nylon through all layers at 2-cm. intervals, with the usual closure by layers where these were identifiable.

During the operation the patient was given a further two bottles of blood and his blood-pressure remained at 130/80. Two more bottles were given post-operatively. His hæmoglobin three hours after operation was 78 per cent.

His recovery was uneventful. Bowel-sounds returned on the third day after the operation. On discharge from hospital his hæmoglobin was 78 per cent and the liver function tests were normal apart from the serum alkaline phosphatase which was raised to 40 units/100 ml.

He was seen again on Feb. 11, 1959, when there were no abnormal findings and the liver function tests were all normal. It is not proposed at present to re-admit him for portacaval anastomosis, but to observe him to see whether he will have any further hæmorrhage.

DISCUSSION

This case would appear to be the first reported in which hæmorrhage had occurred from varices formed in an adhesion. A similar diagnostic problem was, however, described by Levy, Hardin, Shipp, and Keeling (1957) whose patient had varices in the ascending colon and cæcum. In their case no cause for the development of varices at this point was

found, but the patient presented similarly with known portal hypertension and the passage of blood per rectum, and absence of blood from the gastric aspirate. A pre-operative diagnosis of bleeding distal to the pylorus was made.

It seems extraordinary that these varices which must originally have been of capillary size should be able to increase to this diameter. The occurrence of varices in inflammatory adhesions has been remarked upon by Child (1954), but he does not give references for this or quote cases.

It may be expected that to develop varices of this size considerable time is necessary. In this case the time between the operation of splenectomy and the next bleed was seven years. Since each of the three episodes of bleeding after the splenectomy was not accompanied by vomiting it is tempting to suppose that they all occurred from the intestinal varices and not from the œsophageal varices or gastric ulcer. On this basis the decision was made not to do a portacaval anastomosis unless the patient has a further hæmorrhage.

It is impossible to speculate on the number of cases in which varices of this kind could arise on the strength of two cases. However, in cases which present in a similar way to these and, in particular, those having a history of previous operation or intra-abdominal inflammation, the possibility is worth remembering.

SUMMARY

A case is described in which intestinal varices due to portal hypertension were found at laparotomy in an adhesion to an operation scar. The diagnosis was complicated by a previous history of hæmatemesis and of duodenal ulcer. The presenting symptom was bleeding per rectum.

It is suggested that in cases with a similar presentation, particularly those with a history of abdominal operation or inflammation, this possibility should be kept in mind.

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EXTRA-ADRENAL NEUROBLASTOMA

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NEUROBLASTOMAS are not uncommon tumours of childhood. They comprise 14 per cent of all verified tumours occurring at the Hospital for Sick Children in London (Bodian, 1959).

The prognosis of these tumours is generally poor. Bodian in his series had 30 children out of a total of 129 who survived for more than one year (23 per cent) and only 16 (12·4 per cent) who survived for more than three years. Phillips (1953) recorded 7 patients out of 58 (12 per cent) who survived for 5 years or more.

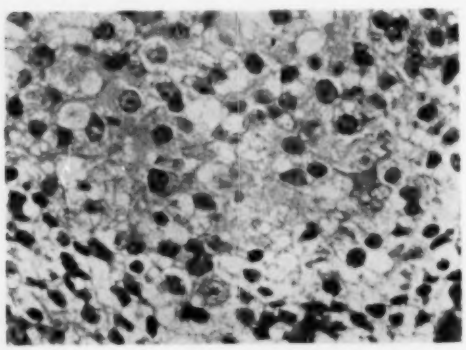

FIG. 488.—*Case* 1. Gland of neck, showing differentiation to form ganglion cells. H. and E. (× 360.)

The prognosis of tumours arising in sites other than the adrenals or abdominal sympathetic chain is, however, substantially better. Bodian reported 9 cases out of 81 (11 per cent) surviving one year for adrenal and abdominal tumours, as compared with 17 cases out of 28 (35·5 per cent) extra-adrenal tumours. Phillips reported 3 cases out of 38 (8 per cent) surviving 3 years in his adrenal and abdominal tumours as compared with 6 cases out of 15 (40 per cent) extra-adrenal tumours.

Of 23 cases seen in the London Hospital Radiotherapy Department from 1948 to 1958, 15 were of adrenal or abdominal origin, 1 of which survived for more than one year (6·5 per cent); 8 cases were of extra-adrenal origin, 5 of which survived for 4 years or more (62 per cent). These 8 patients are now described. (*Cases* 4 and 5 were described originally by Jacobs in 1955.)

CASE REPORTS

Case 1.—This 5-month-old girl developed a swelling in the left side of the neck. A month later, in August, 1949, several large lymph-nodes were found in the left side of the neck. A biopsy was taken elsewhere and reported a lipoid reticulosis. The glands remained the same size until April, 1952, when they started to enlarge again. In May, 1952, when the child was 3 years old, one gland was excised, and the pathological report was neuroblastoma with differentiation to form ganglion cells (*Fig.* 488). The slide of the gland previously excised in 1949 was re-examined and this too was reported as neuroblastoma (these diagnoses were confirmed by the Consultative Histological Panel).

In June, 1952, the child was first seen in the London Hospital Radiotherapy Department. She was a fit child, with a mass of nodes in the left and right upper and middle deep cervical regions. Nothing abnormal was

found in the abdomen. A chest radiograph and intravenous pyelogram were normal. The hæmoglobin was 73 per cent, the white-cell count 7600, with a normal differential count. A course of radiotherapy was given to both sides

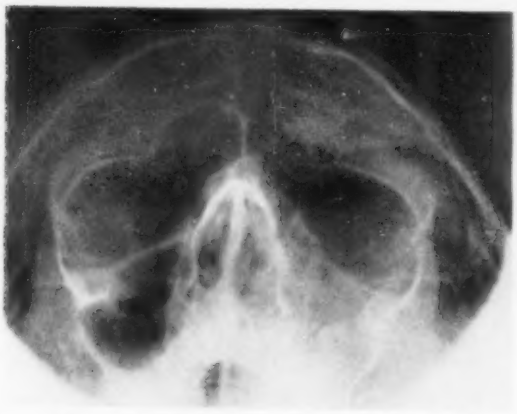

FIG. 489.—*Case* 2. Maxillary antra, showing opacity in the left antrum.

of the neck, using a pair of parallel opposed fields of 10 × 8 cm. at 200 kv. (filtration 0·5 mm. Cu, 1 mm. aluminium), the tumour dose being 2500 r given daily in 20 days. As the nodes were slow to respond a further 1000 r incident dose was given to each side of the neck using 5 cm. circular fields again at 200 kv. in 8 days. Within a month the nodes had almost completely regressed. The child has remained well, apart from some dental caries, which eventually required dental extraction (without complications) in April, 1958. When last seen in March, 1959, she was symptom-free and with no sign of recurrence of her original tumour (a 7-year survival).

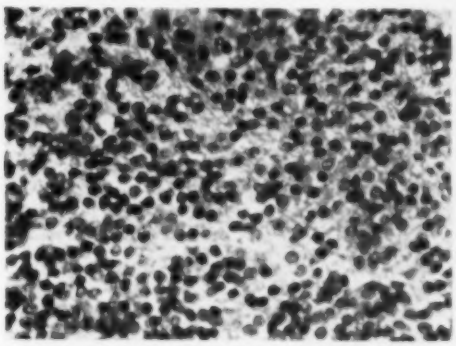

Fig. 490.—*Case* 2. Biopsy from left antrum. Undifferentiated neuroblastoma. H. and E. (× 320.)

Case 2.—This 10-year-old boy had epiphora of the left eye, for which an operation on the lacrimal sac was performed in 1946. Two years later, in 1948, he noticed a blockage of the left side of the nose. In January, 1949, some bony thickening was found over the lacrimal-sac

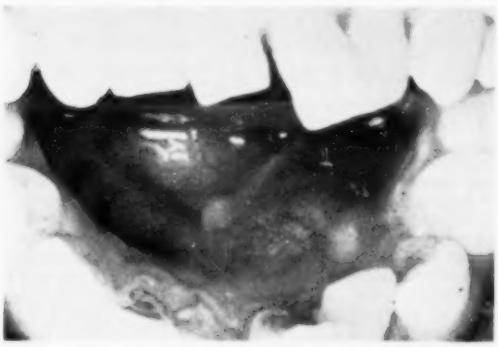

FIG. 491.—*Case* 3. Tumour attached to mandible.

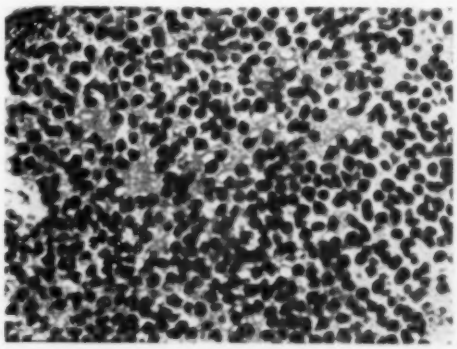

FIG. 492.—*Case* 3. Biopsy of mandibular tumour with rosette formation. H. and E. (× 360.)

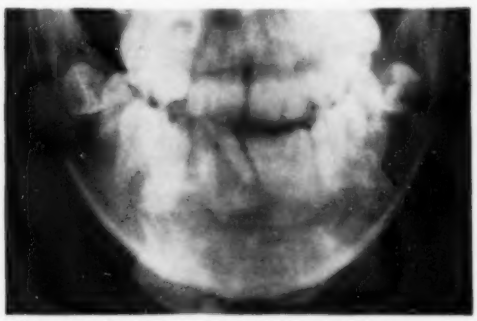

FIG. 493.—*Case* 3. Dec. 16, 1955. Mandible before treatment.

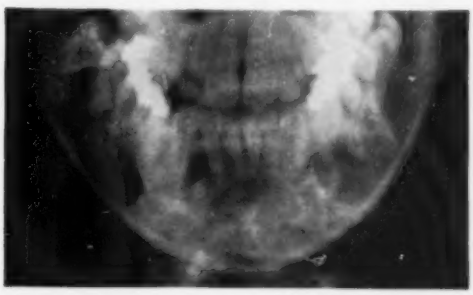

FIG. 494.—*Case* 3. Oct. 14, 1959. Mandible after treatment.

incision. A radiograph taken then showed some opacity in the left antrum (*Fig.* 489). The left nasal obstruction continued, and in January, 1950, a biopsy of the left ethmoid region was carried out elsewhere. The pathological report was that of a low-grade sarcoma.

The boy was first seen in the radiotherapy department in February, 1950. There was a hard swelling in the region of the left antrum, internal to the left inner canthus. The left nostril was blocked. A radiograph showed an opacity of the left frontal, ethmoid, and maxillary sinuses. In March, 1950, the antrum was explored (Mr. Charles Keogh) via the anterior wall. The antrum was filled with polypoid growth, part of which was ulcerated. The growth appeared to be arising in the ethmoid region. The ethmoid walls were enlarged and extending into the floor of the orbit. Biopsies were taken and the pathological report was that of an olfactory neuroblastoma (*Fig.* 490). The diagnosis was supported by the demonstration of neurofibrils with Bielschowsky's silver method.

A course of radiotherapy was given to the left ethmoid and maxillary antrum. Two 6 × 8 cm. wedged fields (30 cm. f.s.d., 200 kv., filtration 0·5 mm. Cu and 1·0 mm. aluminium) were used to give a tumour dose of 3600 r in 18 treatments over 28 days. Two months later, in July, 1950, the swelling to the left of the nose was appreciably smaller, but the boy had occasional bleeding from the nose. In February, 1951, there was no further nose bleeding, no external tumour was seen, and there was no sign of recurrence. In October, 1951, further nose bleeds started and continued until June, 1952, when a polyp was seen in the posterior left nares. An excision biopsy was taken from the region of the upper border of the left middle turbinate and it was thought that all the visible tumour was removed at the time of biopsy. The report was that of neuroblastoma, similar to that removed in 1950. The patient has remained well, and when last seen in March, 1959, was free from any sign of recurrence (a 9-year survival).

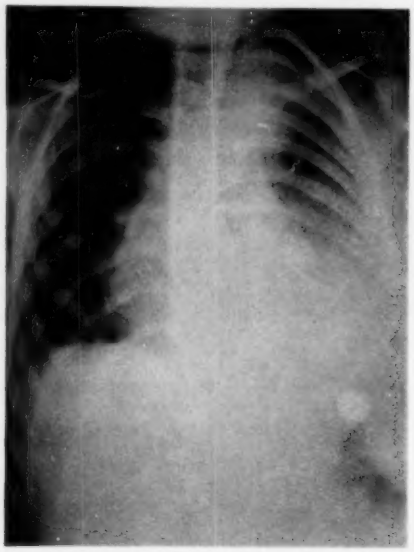

FIG. 495.—*Case* 4. July, 1954. Chest radiograph antero-posterior, before treatment.

FIG. 496.—*Case* 4. July, 1954. Chest radiograph, lateral, before treatment.

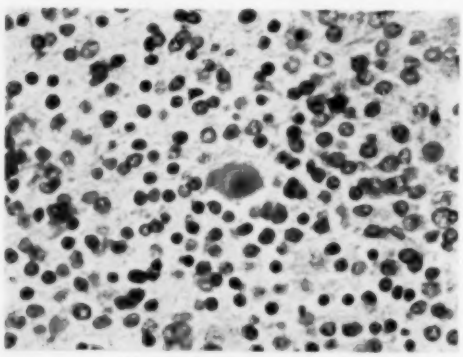

FIG. 497.—*Case* 4. Operation specimen from posterior mediastinum showing differentiation towards ganglioneuroma. H. and E. (× 360.)

Case 3.—This 14-year-old girl noticed a lump at the back of her right lower jaw, with loosening of her right central incisor, in October, 1955. In November, 1955, the lump grew larger, loosening further teeth in the vicinity and causing difficulty with her speech (*Fig.* 491). She attended the dental department where a biopsy of the tumour was carried out (Professor Miles), and the histological report was that of a neuroblastoma (this was confirmed by Professor D. S. Russell) (*Fig.* 492).

When first seen in the radiotherapy department in December, 1955, there was a visible swelling to the right of the symphysis menti, fixed to the bone. In the mouth there was a swelling in the alveolar labial groove extending from the central left incisor back to the region of the premolars; it was plum-coloured and not ulcerated. A similar swelling lay in the floor of the mouth adjacent to the right incisors and canine. There was no peripheral lymphadenopathy, and nothing abnormal was felt in the abdomen. A radiograph of the mandible showed complete bone destruction in the region surrounding the right lower central incisors (*Fig.* 493). A chest radiograph, intravenous pyelogram, and pre-sacral air insufflation

were all negative. There was no Bence Jones proteinuria. The blood-calcium, phosphorus, and alkaline phosphatase were within normal limits. The hæmoglobin was 89 per cent, the white-cell count was 6200, with a normal differential count. A course of radiotherapy was started using a pair of 5 × 5 cm. wedges at right angles to each other (250 kv., 40 f.s.d.; filtration 1 mm. Cu, 1 mm. Al). A tumour dose of 3500 r was given in 15 treatments over 20 days. Two weeks after the treatment finished there was no visible or palpable swelling. The patient has remained well since this time, and when last seen here in October, 1959, was free from any sign of recurrence. The radiograph of the mandible (*Fig.* 494) showed no evidence of tumour (a 4-year survival).

Case 4.—This 2½-year-old girl complained of a chronic unproductive cough in October, 1953. In July, 1954, a radiograph showed a tumour lying in the posterior mediastinum. Areas of calcification were seen within the opacity, and erosion of the inferior surface of the medial part of the left third rib was noted (*Figs.* 495, 496). At operation (Mr. G. Flavell) a tumour was removed from the posterior mediastinum. It was impossible to remove all

FIG. 498.—*Case* 5. Sept., 1953. Chest radiograph, antero-posterior, before treatment.

the tumour as it was invading the arch of the aorta. The histological report was neuroblastoma, differentiating towards ganglioneuroma, with a few definite ganglion cells (*Fig.* 497). Focal calcification of the stroma was present. When first seen in the radiotherapy department in September, the child was well, with no glandular enlargement, no masses palpable in the abdomen, and with a normal blood-count.

A course of radiotherapy was given using a pair of parallel opposed fields to the left chest and mediastinum, 10 × 8 cm. A tumour dose of 3000 r was given in 19 treatments over 24 days (220 kv., filtration 0·5 mm. Cu, 1 mm. Al). In November, 1954, a small left post-operative effusion had cleared and the chest radiograph showed no evidence of recurrence.

When last seen in July, 1959, the chest radiograph was normal, and there was no clinical sign of recurrence of the tumour (a 5-year survival).

Case 5.—This 10-month-old boy was admitted to hospital in September, 1953, complaining of diarrhœa, vomiting, and weakness of the legs for nine weeks. He was found to have signs of spinal-cord compression with a sensory level at the umbilicus. A chest radiograph (*Figs.* 498, 499) showed an opacity in the upper and mid-zones posteriorly. Areas of calcification were seen within the opacity. There was erosion of the posterior part of the fifth left rib.

On Sept. 28 a laminectomy was carried out (Mr. D. W. C. Northfield). A large extradural mass was excised from the region of the mid-dorsal spine. Histologically this was shown to be a differentiating neuroblastoma without any suggestion of ganglion cells (*Fig.* 500).

A course of radiotherapy was given to the tumour site using a pair of 6 × 8 cm. right-angled wedged fields (200 kv.). A tumour dose of 3000 r was given in 16 treatments over 21 days.

The child made a good recovery and was free from abnormal signs by November, 1953. On Jan. 18, 1954, at thoracotomy (Mr. G. Flavell), a firm oval mass overlying the vertebral bodies was removed from the pleura without difficulty. Histology showed pieces of extensively calcified small round-celled neoplasm, probably neuroblastoma.

FIG. 499.—*Case* 5. Sept., 1953. Chest radiograph, lateral, before treatment.

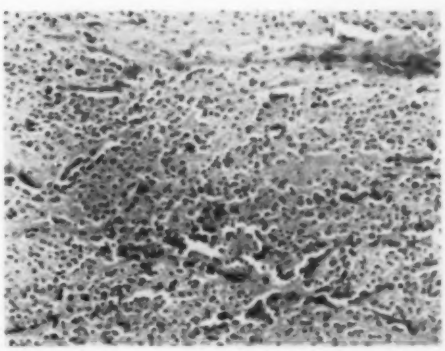

FIG. 500.—*Case* 5. Operation specimen from region of mid-dorsal spine showing rosette formation. H. and E. (× 100.)

In 1953 a marked kyphoscoliosis developed. This has slowly increased and the child suffers from chronic chest infections. When last seen in March, 1959, he was free from any sign of recurrence (a 5½-year survival).

Case 6.—This boy presented, at the age of 9 years, with a year's history of constipation, and two months prior to admission to hospital he had low back pain and severe proctalgia. On examination in August, 1958, there was

limitation of extension of the right hip. There was a patch of anæsthesia over the sacrum and right heel, and the right ankle-jerk was diminished. There was no palpable abdominal mass, but per rectum there was a mass the size of a tangerine, apparently fixed to the right side of the sacrum. A radiograph showed erosion of the right side of the sacrum. The blood-count was normal.

After admission to hospital the pain increased in severity and radiated down the right leg. Retention of urine developed which was partially relieved by carbachol. On Aug. 19 at operation (Mr. D. W. C. Northfield) a non-encapsulated tumour attached to the right side of the sacrum was found. A biopsy was taken. Because of the severe pain a chordotomy was performed at the level of T.4. The biopsy specimen was reported as "an undifferentiated round- and oval-cell tumour probably neuroblastoma". Following the operation the pain was lessened and micturition was normal.

A course of radiotherapy was given to the whole abdomen and pelvis using a pair of parallel opposed fields (220 kv., filtration 1 mm. Al, 0·5 mm. Cu). A tumour dose of 2000 r was given in 30 days. At the same time the boy was given 0·5 mg. of vitamin B_{12}. There was some relief of his symptoms following treatment and he was discharged home on Oct. 3.

A month later he was re-admitted with acute retention of urine, which was relieved by carbachol. The rectal tumour had remained unchanged in size, and a further course of radiotherapy was given to the sacrum, a tumour dose of 2500 r being given in 19 days. This had no effect and the patient's condition slowly deteriorated and he died on Feb. 16, 1959. No post-mortem was performed.

Case 7.—This boy presented, at the age of 4 years, with a 4-month history of a lump in the left side of the neck and blocking of the nose. Subsequently he developed a blood-stained nasal discharge. In September, 1952, at an examination under anæsthesia, a large tumour was found to be arising from the roof of the nasopharynx and there was also tumour palpable in the left side of the nose. A biopsy of these tumours, and from the gland mass in the left side of the neck, was reported as "small polygonal celled malignant tumour probably neuroblastoma".

The child was admitted to the London Hospital in October, 1952. At this time there was a 6 × 6 cm. soft gland mass in the left side of the neck, and a 3 × 2 cm. gland mass in the right side of the neck. There was some swelling of the left orbit. No obvious tumour was seen in the nostril or pharynx. There was no tumour palpable in the abdomen. A skull radiograph was normal and apart from a hæmoglobin of 70 per cent the blood-count was normal.

A course of radiotherapy was given to both sides of the neck using a pair of parallel opposed 15 × 10 cm. fields (220 kv., filtration 1 mm. Al, 0·5 mm. Cu). A tumour dose of 2500 r was given in 18 days. The gland masses quickly resolved, and breathing became normal by January, 1953. However, there was broadening and swelling of the base of the nose and a radiograph of the ethmoid region showed an opacity, but no bone destruction. Residual tumour was thought to be present and a further 2000 r was given by a direct field to the ethmoid region; this produced resolution of the swelling.

In April, 1953, recurrent tumour was present in the glands on both sides of the neck, and metastases occurred in the sacro-iliac region and lumbar spine. These were all treated palliatively with radiotherapy, with some relief of symptoms. The child's condition slowly deteriorated, and he died in July, 1953. No post-mortem was performed.

Case 8.—This boy, at the age of 5 years, had a cough and left-sided chest pain of one month's duration. In August, 1957, a chest radiograph showed a left-sided pleural effusion. At this time he was fairly well, with no palpable abdominal tumour. His blood-count was normal and an intravenous pyelogram showed no abnormality. At thoracotomy on Aug. 12, 1957 (Mr. G. Flavell) a tumour was found adherent to the pleural diaphragm and to the left upper lobe. It was well encapsulated and was completely removed except for its attachment to the apical pleura. Histologically the tumour was reported as an undifferentiated necrotic round-cell malignant neoplasm, probably neuroblastoma.

Post-operatively a course of radiotherapy was given to the whole of the left lung and mediastinum. A pair of parallel opposed 15 × 10 cm. fields were used (250 kv., filtration 1 mm. Al, 1 mm. Cu). A tumour dose of 2000 r was given in 32 days. He was also given vitamin B_{12}, 1 mg. 3 times daily for one month.

He remained symptom-free until 14 months later when in November, 1958, he developed a cough. A radiograph showed a mass at the left apex with destruction of the left second rib, also a rounded opacity at the right costophrenic angle. A further course of radiotherapy was given to the left apex, using a pair of parallel opposed 10 × 10 cm. fields (250 kv.). A tumour dose of 3000 r was given in 27 days. He was also given vitamin B_{12}, 1 mg. 3 times a day.

He remained symptom-free until March, 1959, when his cough recurred. The radiograph showed resolution of the left apical tumour, but an increase of the right costophrenic tumour. He was treated with antibiotics and vitamin B_{12} 1·5 mg. daily. There was some improvement in his cough, but pain was present in the left axilla, and when he was re-admitted to the London Hospital, left Horner's syndrome was noted.

On July 20, 1959, a right thoracotomy was performed (Mr. Flavell) and secondary deposits were found in the upper and lower lobes. A course of radiotherapy to the right lung field was given, using a pair of parallel opposed 20 × 10c m. fields (220 kv.). A tumour dose of 2500 r was given in 29 days with some relief of the cough. The patient developed bronchopneumonia and died in September, 1959. No post-mortem was performed.

DISCUSSION

Neuroblastomas arise from the adrenal medulla and the sympathetic nervous chain, including the distal cell-stations of the autonomic nervous system. These latter may be found in the thorax, abdomen, and pelvis as well as other parts of the body. The commonest site of origin is the adrenal gland and the adjacent sympathetic chain in the abdomen.

In the thorax and pelvis extra-adrenal tumours arise from the sympathetic chain. Those in the neck may involve the adjacent lymph-nodes at an early stage. The tumour in the jaw described in this paper presents a difficult problem with regard to its site of origin. An isolated metastasis from a primary in one of the usual sites is not entirely excluded, but if so, spontaneous regression of the primary tumour must have occurred either previously or while the secondary tumour manifested itself. The only reasonable alternative is that the tumour arose primarily in relation to the submandibular ganglion, which receives a few sympathetic fibres from the superior cervical ganglion via the plexus of the facial artery (Gray, 1954). The tumour then spread directly to involve the mandible, which lies superficially to it.

Olfactory neuroblastomas were first described by Berger in 1924, and 29 cases were recently reviewed by Mendeloff (1957); a further case has lately been reported by Aldave and Gallager (1959). They appear to be more common in adults and adolescents than in children. They usually present with unilateral nasal obstruction, and are of fairly slow growth with

a tendency to spread locally rather than metastasize widely. They are markedly radio-sensitive.

Pathology.—A comprehensive account of the pathology of these tumours has recently been given by Russell and Rubinstein (1959). Macroscopically, the neuroblastomas are large, soft tumours, wholly or partially encapsulated, often with recent hæmorrhage, necrosis, and, more rarely, calcification. Microscopically, they are highly cellular homogenous masses of small, regular cells. Rosettes, which are found in 15–50 per cent of cases, consist of spheroidal groups of nuclei enclosing a delicate network of fibrillary material. The neuritic nature of the fibrillary material is sometimes confirmed by the Bielschowsky silver method. Microscopic invasion of veins and lymphatics may be seen. Stages of differentiation may be found in the same tumour, but there appears to be a tendency for a higher degree of differentiation to occur in those tumours arising in the thorax and pelvis (Bodian, 1959).

Ganglioneuroblastomas, of which *Cases* 1 and 4 may be regarded as examples, are much less common, and appear to be histologically situated between the undifferentiated neuroblastoma and the benign ganglioneuroma. Microscopically they show all stages of differentiation, and rosette-formation may occur in the more primitive areas. Elsewhere, bizarre and multinucleate ganglion cells may be found. These tumours are thought to be more benign than the neuroblastomas.

Histologically the olfactory neuroblastomas consist of closely packed undifferentiated neuroblasts with highly vascular stroma and mixed with leashes of neurofibrils. Their origin is controversial; possibly the neuro-epithelial cells of the olfactory mucosa are responsible.

Spontaneous regression is rare in neuroblastomas, and is estimated to be about 1–2 per cent. Phillips (1953) mentions 5 such cases in 582 and Bodian (1959) 1 in 129. In one case described by Phillips the tumour differentiated into a benign ganglioneuroma and was subsequently excised. A further discussion on this phenomenon has recently appeared (Fox, Davidson, and Thomas, 1959).

Age.—The age incidence in relation to prognosis is described by Sutow (1958). A much worse prognosis is given for those patients presenting for the first time over the age of 2 years. Similarly, the average presenting age of the 3-year survivors treated by conventional therapy was 23 months in Bodian's cases. On the other hand, in this series the average presenting age of the 5-year survivors was 5½ years.

Diagnosis.—Although calcification is a useful radiological diagnostic sign (Jacobs, 1955) an open biopsy is essential in order to obtain a large enough specimen for adequate histological examination.

Treatment.—This may be by surgery, radiotherapy, or a combination of both. The use of vitamin B_{12} has been recently described (Bodian, 1959), and would appear to be most effective in children under 1 year of age. In this series only 1 patient (*Case* 8) was given vitamin B_{12}, but without effect.

Since radiotherapy alone may fail to cure the tumour, as in *Cases* 2, 7, and 8, then, if operable, surgery should be considered as the first method of treatment. That this can be curative is shown in 2 patients in this series (*Cases* 2 and 5). Wittenborg (1950) has also reported the effectiveness of this method of treatment.

However, in some instances the tumour cannot be completely excised. In these cases a full post-operative course of radiotherapy should be given, and in this series this combination of treatment was curative in 1 patient (*Case* 4).

As neuroblastomas are fairly radio-sensitive, if the tumour is inoperable or surgery is contra-indicated, then a full radical course of radiotherapy should be given. This eradicated the tumour in 2 patients in this series (*Cases* 1 and 3) and was shown to be a useful method of treatment by Phillips (1953).

If a radical course of radiotherapy is being considered, then a tumour dose of 2500–3500 r should be given in a period of 3–5 weeks, depending on the volume to be irradiated, and the age of the patient. The systemic effect of irradiation of the extra-adrenal sites to this dose level is not severe, particularly if the irradiated volume is not unduly large.

SUMMARY

1. Eight cases of extra-adrenal neuroblastoma, of which 5 survived for more than 4 years, are presented. In 2 of these there was histological evidence of ganglion-cell differentiation.

2. The improved prognosis of neuroblastoma arising in sites other than the adrenal gland or abdomen is emphasized.

3. The present methods of treatment are briefly discussed.

I would like to thank Dr. J. A. Orr and Dr. L. J. Rubinstein for their help and advice; Professor Miles, Mr. Charles Keogh, Mr. D. W. C. Northfield, and Mr. G. Flavell for permission to publish their cases; and Professor D. S. Russell for permission to publish the histological reports.

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A REPORT ON 313 INGUINAL HERNIÆ REPAIRED WITH NYLON NETS

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No method of herniorrhaphy yet published is free from a number of recurrences. Surgeons agree that the number of recurrences increases with the mounting age of the patients, and that the risk of a recurrence is greater, at all ages, for a direct type of hernia than for an indirect. They also agree that the risk of a recurrence is maximal when the hernia is due to a previous unsuccessful repair (Grace and Johnson, 1937; Fallis, 1936, 1937; Shelley 1940 a, b; Wakeley, 1940).

In an attempt to improve their results surgeons have, from time to time, sought to strengthen the inguinal canal by sewing a foreign body into it, or by darning its posterior wall with non-absorbable sutures.

McGavin (1909) advocated the insertion of a silver wire filigree into the inguinal canal, a method later adopted by Cole (1941), and by Ball (1958) of the Alfred Hospital, Melbourne.

More recently a tantalum wire mesh has been introduced (Douglas, 1948; Koontz, 1948; Throckmorton, 1948; Burnell, 1954), and so has polyvinyl alcohol sponge (Schofield, 1955). A hand-made silk net was employed by our colleague, the late John Stretton (1948). A polyethylene plate was used by Thompson (1948) and a vitallium plate by McNealy and Glassman (1950).

The canal has been repaired with pieces of nylon material by Stock (1954) and by Horwich (1958).

Handley (1918) darned the posterior wall of the inguinal canal with silk; Abel and Hunt (1948) did the same with stainless steel wire, and at Oxford nylon has been used (Moloney, Gill, and Barclay, 1948; Moloney, 1958).

In spite of all these trials, extending over fifty years, the search for the ideal material for 'inlay grafting' in this condition continues (Capper, 1953).

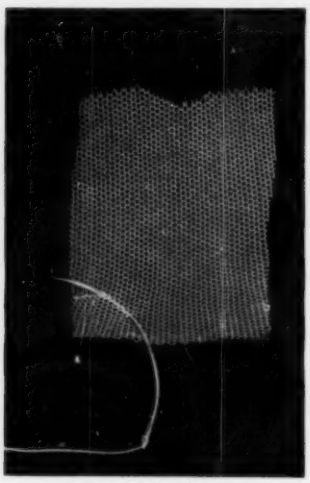

FIG. 501.—The thin net.

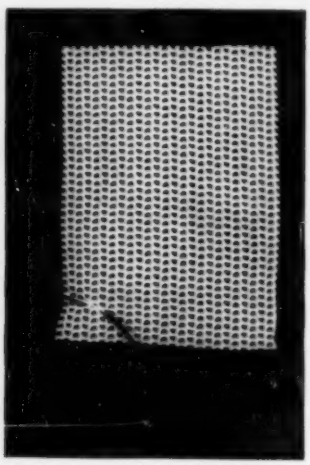

FIG. 502.—The thick net (Stock, 1954).

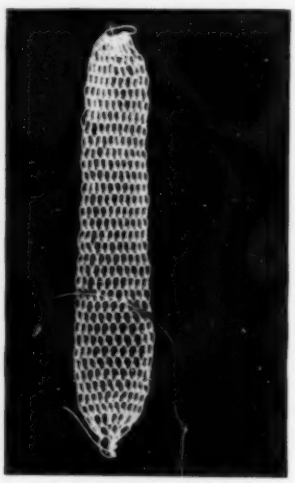

FIG. 503.—The medium net.

The present report is an account of our experience with three different kinds of nylon net in the treatment of inguinal herniæ, indirect, direct, and recurrent.

TYPES OF NET

The three kinds of netting differed mainly in the thickness of the strand from which each type was made, and in the closeness of the weave. In the following report the nets are referred to as the 'thin net' (*Fig.* 501), the 'thick net' (*Fig.* 502), and the 'medium net' (*Fig.* 503). The 'medium net' is a replica of Stretton's silk net made in nylon by our theatre staff; the 'thick net' is the one introduced by Stock (1954), who used it on 10 patients with inguinal hernia and 2 other cases.

RESULT OF TEST

Thin Net.—This net, consisting of fine undyed curtain netting, was regarded as a substitute for the transversalis muscle fascia (Lytle, 1945), and sewn into the position normally occupied by that structure, with interrupted fine monofilament nylon sutures, its upper border being pulled up, for an inch, above the margin of the conjoined tendon on its deep aspect. It was used to repair 86 inguinal herniæ in the years 1951 to 1954 inclusive; 83 were in men and 3 were in

women; 73 of the patients were over 50 years of age, the other 13 being younger. Of these 86 inguinal herniæ, 50 were primary indirect inguinal, 14 were direct, and 22 were recurrent.

The wounds were soundly healed within 14 days in 81 instances, but in 5 they became septic. Of the 5 septic wounds, 3 were soundly healed within a month, 1 took two months to heal, and the remaining one never healed, the net having to be removed.

To assess the value of this procedure a 2-year follow-up was carried out, the patients being examined at intervals of six months up to two years, but not thereafter. The results were bad. Only 67 out of the 86 herniæ were observed for two years, and out of the 67 which were examined 19 recurrences were found. Out of 36 patients with primary indirect inguinal herniæ who attended 8 had recurred; of the 11 direct inguinal herniæ, 3 had recurred; and of the 20 recurrent herniæ 8 had developed a further recurrence. This net was therefore discarded as unsatisfactory.

Thick Net (Stock, 1954).—A short trial was given to this net in 1954–5, with disastrous results. It was used in 15 cases—6 primary indirect inguinal herniæ, 2 primary direct herniæ, and 7 recurrent inguinal herniæ. Of these cases, 11 of the patients were over 50 years of age and 4 were younger. Out of these 15 cases only 6 wounds healed soundly in 14 days, 1 wound dried up after having a discharging sinus for 6 months, and the remaining 8 wounds did not heal until each of the nets had been removed. All the 8 septic-net wounds were given 6 months in which to heal before arrangements were made to remove them. As the result of this experience the trial was abandoned.

Medium Net.—Of the three kinds of netting tested this alone promises to be of some value in the repair of inguinal herniæ. It was inserted into 212 herniæ of this type in 182 patients during the years 1954 to 1957 inclusive; 174 of the patients were men and 8 were women. In age, 114 of the patients were over 50 years old and 68 were younger. Of these herniæ 110 were primary indirect, 68 were primary direct, and 34 were recurrent in type.

Unlike the thin net, the medium net was not regarded as a substitute for the transversalis muscle fascia; it was inserted superficially to the plane of that fascia and also to the plane of the conjoined tendon and internal oblique muscle. This net was sewn into position with continuous undyed braided nylon sutures (6 lb. in tensile strength), the lower edge being secured to the deep aspect of the inguinal ligament from the pubic spine to a point 1 in. lateral to the site of the deep abdominal ring. The upper edge was not pulled up on to the deep aspect of the conjoined tendon, as had been done with the 'thin' net, but was sewn on to the superficial surface of the conjoined tendon and internal oblique muscle, ¾–1 in. above their arching free margin. The cord was brought out under the lower edge of the net, half-way between the pubic spine and the anterior superior iliac spine (*Fig.* 504).

The incisions were soundly healed within 14 days in 196 out of the 212 herniæ into which the medium net had been inserted; 13 wounds required from 15 to 28 days to heal, and 3 did not heal. Three incisions which healed broke down later, making a total of 6 septic wounds; in each of these septic cases the net had to be excised to achieve healing of the wound concerned.

As with the two other types of net being tested, assessment has been based on a 2-year follow-up. Of the 212 inguinal herniæ repaired with the medium hand-made nylon net 195 (91·9 per cent) were successfully followed for two years; 17, however, were lost, 6 due to death from intercurrent disease unconnected with the repair of their herniæ. In these 195 repairs there were 10 failures, 4 being recurrences and 6 being septic wounds from which the net had to be removed. It is possible, however, that all of the 17 patients whom we were unable to trace at two years have recurred, but it is unlikely, in view of our experience as a whole, that any of them will have become septic, because even in the 3 wounds which healed and broke down later, they did so within a few weeks of the operation. It is probable, therefore, that we are aware of all the septic wounds in this series and are in a position to state that the 'sepsis rate' has been 2·83 per cent (6 instances in 212 repairs). As 'sepsis' here refers to chronic sinuses it cannot be usefully compared to the published incidence of wound sepsis following the use of absorbable sutures.

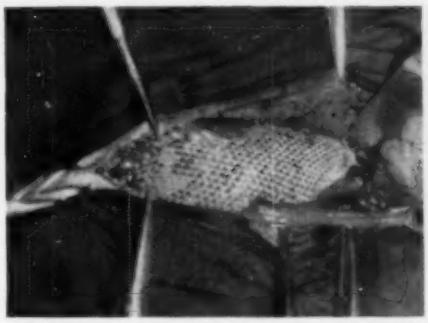

FIG. 504.—A right inguinal hernia repaired with a medium net. The cord emerges between the net and the inguinal ligament; the tip of the retractor rests on the pubic spine.

The position with regard to the rate of recurrence is not determinable because of the 17 cases which were untraced at two years from the time of operation, and because 6 nets had to be taken out. Excluding the 6 septic cases, 189 out of 206 repairs which remained free from sepsis were examined at two years, and only 4 recurrences were found. It is possible that these 4 recurrences represent the total, a recurrence rate of 1·9 per cent; but it is also possible that all the 17 repairs which were not examined have, in fact, recurred, which would raise the rate of recurrence of 11·1 per cent.

Not all the septic cases from which the nets were removed had recurred when they were examined after two years, but this freedom from recurrence ought to be regarded as a success for Nature, not for surgery. From the surgical standpoint these 6 septic cases are failures because the nylon net had to be taken out, and as failures they should be added to those uninfected cases which are failures because the hernia has recurred. On this basis there have been

10 failures, 6 septic nets and 4 uninfected recurrences, out of the 212 herniæ operated upon. This would be a failure rate of 4·7 per cent, and if the 17 cases which were not examined are also failures due to recurrence, as they may be, the failure rate rises to 12·7 per cent. It would seem that the correct way to express the result of this test with the medium net is to state that normal mode of life. Eleven instances of testicular atrophy were found, an incidence of 5·9 per cent.

DISCUSSION

Because of past experience many surgeons disapprove of the implantation of foreign bodies into living tissues. Most foreign bodies are tissue irritants

FIG. 505.—Scar in rabbit muscle round nylon netting. Upper half of figure shows dense scar tissue containing atrophic muscle. Lower half shows œdematous scar tissue and site of nylon. (× 45.)

FIG. 506.—Same field as in *Fig.* 505 under polarizing microscope, showing nylon fibres (white). To show background, the light was incompletely polarized. (× 45.)

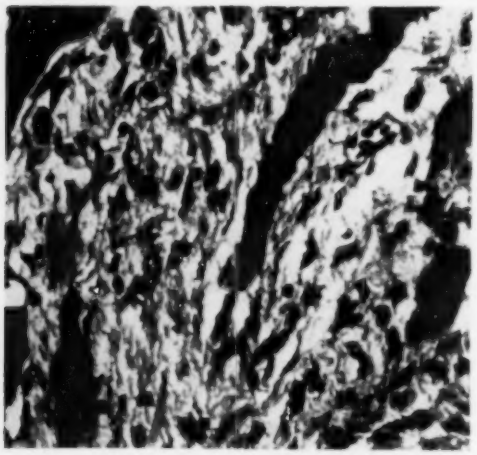

FIG. 507.—Rabbit. Dense scar tissue involving muscle. (× 350.)

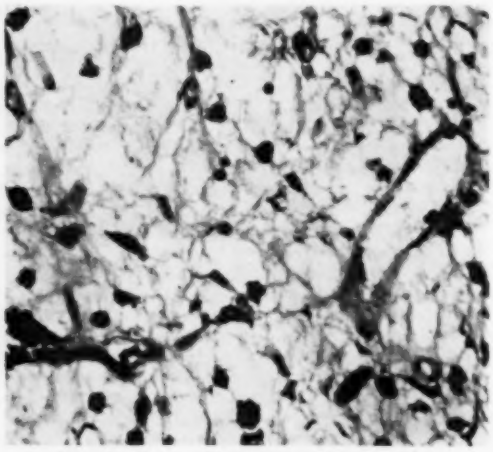

FIG. 508.—Rabbit. Œdematous scar tissue near nylon. (× 350.)

in 212 repairs the number of failures could be 10 (4·7 per cent) or it could be 27 (12·7 per cent).

Morbidity.—In this test using the medium net there were 185 repairs examined at two years which were free both from sepsis and from recurrence. Only 1 patient complained of persistent pain, not in the groin but in the testicle, and there were 19 who said they suffered an 'occasional ache', or an 'occasional twinge'. None of these patients had, on this account, changed their work or altered their

and delay the healing of the wound; the reason why they have this noxious effect is well known.

The process of healing occurs in two phases; first, the physico-chemical inflammatory stage, when the irritation due to the damaged cells initiates the process of autolysis and phagocytosis by which they are removed; the second stage is the process of repair. (Dible, 1950.) In an aseptic incised wound these two phases are completed in about fourteen days. As the stage of repair follows the stage of

inflammation, anything which prolongs the inflammatory stage inevitably delays the stage of repair. Infection of the wound by bacteria prolongs the inflammatory phase because the bacteria, being able to proliferate, maintain a continuous act of trauma, which delays the stage of repair and the healing of the wound (Arey, 1936; Localio, Casale, and Hinton, 1943a, b).

A foreign body, if it is an irritant, produces a substance by chemical interaction with the tissues which kills cells; the dead cells stimulate the inflammatory process necessary for their removal, and it will continue as long as the irritating foreign material lasts. Such a foreign body, if it is not absorbed or extruded, may indefinitely delay the phase of repair. If a wound containing an irritating foreign body becomes infected by bacteria the inflammatory process is aggravated, because it is being stimulated, both by the cells which have been killed by the foreign body, and by an additional number of cells which have been killed by the bacteria (Localio and others).

The justification for inserting nylon into the tissues is the belief that it does not lengthen the inflammatory stage of wound healing, because, being inert, it does not interact chemically with those tissues to produce a substance which kills cells. Most investigators have reported that nylon produces hardly any inflammatory response in living tissues (Aries, 1941; Localio and others; Blaine, 1946). Two reports, however, speak of nylon as a strong tissue irritant (Large, 1943; LeVeen and Barberio, 1949), and nylon clothing can irritate the skin, but such dermatitis is rare and often due to a dye and not to the nylon itself (Calnan and Wilson, 1956). In addition, plasticizers added to nylon during manufacture may be strong irritants (Blaine, 1946).

From our experience with experimental animals we agree with those authors who have reported that nylon is almost inert and does not interact with living tissues. We implanted strips of the thin nylon net into the erector spinæ muscles of 4 rabbits under aseptic surgical conditions. Ten days later the animals were killed, the appropriate piece of muscle excised, and sections stained with hæmalum and eosin were prepared. They had the following histological appearances. The scar tissue adjoining the inserted material was œdematous, but leucocytes of all types were scanty or absent. There was no sign of infection. The surrounding muscle was penetrated by scar tissue and appeared atrophic; some muscle-fibres contained several vacuoles of unequal size, several being large. Multinucleated foreign-body giant cells were scattered in small numbers near the inserted material; these cells may have been derived from muscle, since all intermediate appearances were seen (*Figs.* 505–508).

The small amount of human material which has been examined tends to confirm the experimental findings. An inguinal canal containing a thin net was recovered eighteen months after the operation from a patient who died of pyelonephritis. It was found that the net was sandwiched between two soft, delicate, thin, whitish layers of fibrous tissue and that there was no induration. The net had become incorporated in this fascia by the growth of the fibrous tendrils through the openings in the net, the union being so intimate that a strong light and a magnifying glass were needed to identify it, and an attempt to dissect out the net failed completely. There was no suspicion of any inflammatory reaction to be seen.

Recently, two groins containing the medium net were obtained from a man who died of a coronary thrombosis on the fourth post-operative day. The two specimens showed no histological evidence of a reaction to the nylon.

In addition to nylon, stainless steel wire (Babcock, 1935), tantalum, polyvinyl sponge, and polyethylene have been said to be almost inert; so have vitallium (Venables, Stuck, and Beech, 1937) and titanium (Bothe, Beaton, and Davenport, 1940), both of which can be securely lodged even in living bone. Nevertheless, the innocuous nature claimed for certain foreign bodies has sometimes been belied by clinical experience.

Out of the 313 nylon net repairs in this report, 15 resulted in chronic septic sinuses (4·8 per cent). It is evident, therefore, that in a certain proportion of patients there may be an inflammatory reaction between the tissues and the contained nylon net. Our experience suggests that the quantity of nylon which can safely be inserted is limited. This statement rests on the fact that out of 83 thin nets there was only 1 chronic sinus (1·2 per cent); that in 212 medium-net repairs there were 6 chronic sinuses (2·83 per cent); but that with the thick net there were 8 chronic sinuses out of 15 repairs (53·3 per cent).

Each of these 15 chronic sinuses had to be opened and the nylon net removed. The appearance of the tissues was similar in each case, the inguinal canal being filled by a bulky, iron-hard mass of fibrous tissue containing pockets of pus. Sometimes the net was loose, floating in a pool of pus; at other times the net could not be identified, the whole indurated mass having to be excised in order to remove it. The histological report on one such case is typical of them all. In this case the specimen consisted of fibro-fatty tissue containing an old scar. The scar was composed of dense, cellular, wavy, fibrous tissue enclosing a mass of suture material, which was permeated and surrounded by many multi-nucleated foreign-body giant cells. The neighbouring scar tissue contained large groups of plasma cells, and in places there were also numerous polymorphs. The picture was therefore that of a foreign-body reaction complicated by secondary infection.

The secondary infection in 14 of the 15 chronic sinuses was due to a coagulase-positive *Staphylococcus pyogenes*. From the other patient a very resistant diphtheroid bacillus was grown. The *Staph. pyogenes* was resistant to penicillin in 7 of the 14 wounds from which it was cultured, and it was only slightly sensitive to it in 2 other instances. Two of these staphylococci were resistant to streptomycin, and 4 others were individually insensitive to aureomycin, terramycin, and tetracycline. Chloromycetin suffered least from the defect of bacterial resistance.

However, in spite of the fact that the invading *Staph. pyogenes* remained sensitive to at least one of the antibiotics in every case, the administration of the appropriate substance failed to eradicate the sepsis while the net was in situ.

In our opinion this infection occurred during the operation. In support of this view is the fact that only

1 wound had become inflamed by the seventh post-operative day; 6 were discharging on the tenth day, 5 did not break down until the fourteenth to twenty-first day, and 1 gave no trouble until six months after the net had been put in. In each case the infection seemed to occur in the depth of the wound, there being no evidence to suggest that it had occurred superficially and then burrowed down to the net. Nor was there evidence of systemic infection at the time the sepsis developed.

The contamination of a wound containing a nylon net by pyogenic organisms is serious. If nylon were absolutely inert it would not prolong the inflammatory phase of healing in a septic wound; but although it may be absolutely inert in the tissues of some patients it is obvious that this is not always so. Moreover, our experience suggests that the quantity of nylon buried in some of the wounds which healed soundly must have been dangerously near the limit of tolerance. This seems the most likely explanation of the fact that 5 out of the 15 chronic sinuses occurred in patients who had had a bilateral operation, the sepsis in each of the 5 cases being confined to one side. Evidently in these patients the wound was just able to tolerate the nylon, but unable to overcome the additional physico-chemical trauma due to a bacterial invasion.

CONCLUSIONS

The medium (hand-made) nylon net may prove a useful addition to surgical technique in the repair of inguinal herniæ.

As some patients may have an idiosyncrasy to nylon a preliminary patch test is advisable.

As nylon is a slightly irritant foreign body the quantity which can safely be inserted into living tissues is probably limited.

Great care with regard to asepsis, in all its aspects, should be practised when a nylon net is to be used in the repair of an inguinal hernia.

SUMMARY

The search for a foreign body suitable for repairing inguinal herniæ is outlined.

Three types of nylon net are described. These we have used in the years 1951–7 inclusive to repair 313 inguinal herniæ, primary and recurrent, indirect and direct.

Thin nets: 86 were used with a sepsis rate of 1·2 per cent and a 2-year recurrence rate of over 20 per cent.

Thick nets: 15 were employed with a sepsis rate of 53·3 per cent. Test abandoned.

Medium nets: 212 were employed with a sepsis rate of 2·83 per cent and a failure rate (recurrences plus removals of net) ranging from a minimum of 4·7 per cent to a possible maximum of 12·7 per cent.

The belief that nylon is an inert substance which does not damage living tissues due to a noxious chemical interaction is discussed. Experimental and clinical evidence is described, suggesting that some persons may have an idiosyncrasy towards it, and that the amount of nylon which normal tissues will tolerate is probably limited.

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EXPERIMENTAL SURGERY

A CLINICAL AND EXPERIMENTAL STUDY OF FUNCTIONAL PARALYSIS OF THE FACIAL NERVE FOLLOWING CONSERVATIVE PAROTIDECTOMY

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SOME form of conservative parotidectomy, i.e., parotidectomy with conservation of the facial nerve, is now a standard procedure in diseases of the parotid gland. Following these operations, patients frequently have a temporary facial paralysis, which in view of the anatomical preservation of the nerve may be termed 'functional'. This paper reports a study of such functional facial paralysis with special reference to its incidence, causation, and possible prevention. In the first part of the paper we analyse the incidence and degree of functional facial paralysis in 95 consecutive cases of conservative parotidectomy. In the second we report the results of an attempt to transfer the problem to the experimental laboratory. Finally, we consider the practical implications of our findings.

Table I.—INCIDENCE OF FACIAL PARALYSIS IN 95 CASES OF CONSERVATIVE PAROTIDECTOMY.

Grade I	51 cases	(54 per cent)
Grade II	31 cases	(32 per cent)
Grade III	13 cases	(14 per cent)
	95	

Table II.—INFLUENCE OF TYPE OF OPERATION ON INCIDENCE OF PARALYSIS

	Total Parotidectomy	*Superfacial Parotidectomy*	
Grade I	13 cases (42 per cent)	38 cases (59 per cent)	
Grade II	9 cases (29 per cent)	22 cases (34 per cent)	
Grade III	9 cases (29 per cent)	4 cases (6 per cent)	$\chi^2 = 11$, $P = .001$
	31	64	

Table III.—INFLUENCE OF IRRIGATION OF WOUND WITH PERCHLORIDE OF MERCURY ON INCIDENCE OF PARALYSIS

	Perchloride	*No Perchloride*	
Grade I	10 cases (38 per cent)	41 cases (59 per cent)	
Grade II	8 cases (31 per cent)	23 cases (33 per cent)	
Grade III	8 cases (31 per cent)	5 cases (7 per cent)	$\chi^2 = 6.3$; $P < .02$
	26	69	

CLINICAL

Table I analyses the incidence and degree of facial paralysis in 95 consecutive cases of conservative parotidectomy. Patients were classified as Grade I if, on discharge from hospital, either they had no facial paralysis or facial expression was so near normal that it was unlikely to give rise to comment during ordinary activities. We did not, however, regard weakness of depression of the angle of the mouth as by itself excluding a patient from Grade I, since the submandibular branch of the facial nerve is particularly liable to temporary interruption of its conductivity from any manipulation in the neighbourhood. Grade II indicates that facial movements were present but were grossly and obviously weak. Grade III indicates complete or substantially complete paralysis. Complete paralysis persisting for a week or ten days was always associated with the reaction of degeneration on strength-duration electrical testing. The classification of an intermediate case as Grade I or Grade II was sometimes difficult, depending as it did on a subjective assessment of the degree of facial weakness. The cases classified as Grade III, however, constitute a clear-cut objectively determinable group. Facial paralysis classified as Grade I usually cleared up within a few weeks; that of Grade II within a couple of months; but that of Grade III did not begin to show improvement until two to three months after operation, and might take up to six months to clear up completely. The incidence of Grade III paralysis, which is used in the analyses, is the best index of the predisposing influence of any given factor. At the same time it should not be forgotten that a Grade II paralysis is also an appreciable cosmetic disability.

Analysis of Operative Procedures.—In 31 of the 95 patients the operation performed was a total parotidectomy; in the remaining 64 a partial, usually superfacial, parotidectomy—i.e., removal of the parotid superficial to the facial nerve. *Table II* gives the comparative incidence of the different grades of facial paralysis in the two groups. The 29 per cent incidence of Grade III paralysis following total parotidectomy as compared with 6 per cent following superfacial parotidectomy shows, as would be expected, the predisposing influence of the former operation.

Other Factors.—The figures have been analysed in other ways, but the only other factor found to have an influence on the incidence of facial paralysis was

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irrigation with perchloride of mercury. In view of the evidence of the frequency of implantation as a cause of recurrence following enucleation of parotid tumours (Patey and Thackray, 1958), and influenced by the present trend towards local chemotherapy as a possible preventive measure for such recurrences, a few years ago we began irrigating wounds after parotidectomy for tumours with 1–1000 or 1–500 perchloride of mercury. *Table III* gives the incidence of the different grades of facial paralysis in 26 consecutive cases of all types of conservative parotidectomy in which such irrigation was performed, as compared with that in 69 cases in which perchloride was not used. The 31 per cent incidence of Grade III

FIG. 509.—Lateral view of left side of rabbit's skull. The forceps are pointing to the stylomastoid foramen.

paralysis in the former group as compared with 7 per cent in the latter shows the predisposing influence of the perchloride irrigation. Considering only the 11 cases of total parotidectomy in which perchloride irrigation was also used, 6 showed Grade III paralysis, this extremely high incidence being presumably a summation effect. In view of these findings we abandoned perchloride irrigation. Its use after parotidectomy was in any case probably redundant. For the same reasons, the use of other local chemotherapeutic agents after conservative parotidectomy is probably also contra-indicated.

Permanent Facial Paralysis.—The accepted view is that functional facial paralysis after conservative parotidectomy always recovers completely. In general our experience confirms this view. There were, however, 3 patients in this series with some degree of permanent facial paralysis:—

The first was a woman, aged 28 years, operated on in July, 1957, for a recurrent mixed tumour in the subfacial parotid, which had also been treated by radium. We performed a total parotidectomy, and the operation was followed by a Grade III paralysis. Recovery slowly occurred but was incomplete. The patient has returned to her home in Rhodesia, but from correspondence and photographs we would assess the residual paralysis as Grade I. Perchloride irrigation was used in this case.

The second patient also had a recurrent mixed tumour. She had had four previous operations as well as radiotherapy. A total parotidectomy followed by perchloride irrigation was performed in February, 1958. A Grade III facial paralysis followed, from which recovery slowly occurred, but she still has a Grade II paralysis.

The third patient had a primary mixed parotid tumour with a large retropharyngeal extension. A biopsy through the palate had been performed elsewhere and the tumour was adherent and microscopically infiltrating at this point. Total parotidectomy was performed with excision of the involved portion of palate. Though the facial nerve was preserved it was grossly stretched during the course of what proved to be difficult manipulations, and was much thinner and longer than when first exposed. No perchloride was used. After operation the patient had a Grade III paralysis, which has persisted unaltered.

In the first two patients it is possible that the persistence of some degree of facial paralysis was

FIG. 510.—Dissection of the left facial nerve of the rabbit. The forceps are pointing to the trunk of the facial nerve at the point of its emergence from the stylomastoid foramen. Running horizontally forwards are the two nerves to the region of the mouth and nose; upwards, the nerve to the eyelids; and, backwards, the nerves to the muscles of the ear. The photograph also shows the large size of the vein running vertically immediately deep to the trunk and main branches of the nerve.

related to the combination of the perchloride irrigation with a total parotidectomy, and might not have happened without the perchloride. In the third case perchloride was not used, but the obvious stretching of the nerve must have been associated with gross intraneural disorganization. In a future case of this type, if the danger of stretching seems great and unavoidable, it might be better to cut the trunk of the facial nerve and suture it at the end of the operation. But on the main issue, particularly if it is accepted that in the first two cases permanent facial paralysis might have been avoided, and that the third case should not strictly be classified as functional, the generally accepted view that functional facial paralysis after conservative parotidectomy will be only temporary may still be regarded as substantially correct.

EXPERIMENTAL

Though the operative procedures for parotid disease are limited and fairly standardized, the pathological conditions for which they are performed vary, as also do the difficulties of operation. In addition, the problem in man for obvious therapeutic reasons can only be studied for the most part analytically. It was therefore decided to transfer the

problem to the experimental laboratory. The rabbit was chosen as the experimental animal. The facial nerve of the rabbit is comparable anatomically to that of man, and is large enough for dissection without special difficulty. The stylomastoid foramen of the rabbit is on the lateral side of the posterior skull mass (*Fig.* 509). The trunk of the facial nerve on emerging from the foramen runs outwards and forwards to enter the parotid and curve around the ascending ramus of the lower jaw and the large masseter muscle (*Fig.* 510). In so doing, it runs as in man (Patey and Ranger, 1957) superficial to the main intraparotid venous plane, represented in the rabbit by a particularly large venous trunk. As it curves around the venous trunk it divides into two main divisions: a lower, which almost immediately divides into two and runs horizontally forwards on the masseter to supply the region of the mouth and lower face; and an upper, which runs obliquely forwards and upwards to supply the eyelids and upper face. There are also smaller easily identifiable branches running downwards to the neck. The upper main division divides into a network of small branches which are obscured by areolar fatty tissue and more difficult to free individually than the branches of the lower main division. The most obvious difference between the anatomy of the facial nerve in the rabbit and in man is the existence of large branches supplying the muscles of the ear, which run directly backwards from the main trunk shortly after its emergence from the stylomastoid foramen. All these nerves are well shown in *Fig.* 510.

The eye gives the most accurate indication of facial paralysis in the rabbit, since there is a well-developed nictitating membrane. On stimulation of the conjunctiva or cornea in the presence of facial paralysis, the nictitating membrane, the action of which is normally hidden by the closure of the eyelids, can be seen sliding from before backwards to cover the eyeball (*Fig.* 511). Paralysis of the facial muscles around the mouth is more difficult to detect owing to passive transference of movement from the opposite side, and the ears, too, are an unreliable index owing to the habit of tame rabbits of voluntarily holding their ears in bizarre asymmetrical positions for long periods of time. We therefore relied on the eye as the index of facial paralysis.

Direct Trauma.—In the first group of experiments we submitted the trunk and main branches of the facial nerve to various types of measured direct mechanical trauma. The animals were anæsthetized with pentothal and ether, an incision made from the base of the ear forwards across the cheek, the branches of the nerve to the mouth identified on the masseter, and the trunk exposed back to the stylomastoid foramen by splitting the parotid. We found that the trunk and main branches of the facial nerve were surprisingly insensitive to mechanical trauma, and we were compelled to use more and more vigorous means to produce paralysis. Eventually we adopted two standard methods. In the first one, we pressed the head of a fine dental drill with firm one-finger pressure downwards on to the facial nerve as it emerged from the stylomastoid foramen, and at the same time pressed forwards on to the two main branches. By increasing the number of times pressure was applied, it was hoped that a rough gradation of trauma would be achieved. In the second method the solid nozzle of a modified metal ear syringe was allowed to rest on the trunk of the facial nerve as it emerged from the stylomastoid foramen, and a weight allowed to fall freely the length of the barrel of the syringe. The syringe weighed 330 g., the weight that was allowed to fall was 16 g., and the length of fall 9 cm. The number of times the

FIG. 511.—The conjunctiva of the left eye of a rabbit with facial paralysis is being stimulated with the end of a glass pipette. The absence of contraction of the eyelids enables the nictitating membrane to be seen as it folds over the eyeball from before backwards.

weight was allowed to fall was felt to constitute a fairly accurate gradation of trauma. We are not reporting these experiments in detail, but, as an index of how insensitive the facial nerve was to both these types of direct trauma, there was sometimes no paralysis after the pressure of the dental drill had been applied 50 or more times; and, following the second method, no paralysis was produced when the weight was dropped 50 times or less, and only in about half the operations when the weight was dropped 75 or 100 times. The conclusion was obvious that the trunk and main branches of the facial nerve of the rabbit are resistant to degrees of direct mechanical trauma far beyond those to which the human facial nerve is submitted during conservative parotidectomy.

Experimental Parotidectomy.—We next investigated the effect on the facial nerve of the rabbit of the two main types of parotidectomy performed in man—superficial parotidectomy and total parotidectomy. We found, however, that during removal of the gland we frequently got into trouble with bleeding, and so we modified the procedures so that they were equivalent in their action on the facial nerve to parotidectomies but without actual removal of parotid tissue. For superficial parotidectomy we substituted splitting the gland in the line of the nerves to the mouth, and peeling back each half of the superficial parotid upwards or downwards from off the facial nerve and its branches. The nerves thus lay free superficially but undisturbed on their deep surface. For the equivalent of total parotidectomy, we added to the above procedure the freeing of the nerve and its main divisions on their deep surface up to and including the beginning of the terminal branches. A long length of facial nerve and its branches thus lay

completely free from surrounding tissues as after total parotidectomy.

The effects on the facial nerve of the two procedures were different. The superfacial parotidectomy equivalent procedure occasionally produced facial paralysis; the total parotidectomy equivalent very frequently. Thus, whereas in 17 of the former operations there were only 4 paralyses, in 36 of the latter there were 30 paralyses. The experiments thus confirmed the clinical finding that an important factor in producing the paralysis was something that happened to the nerve when it was completely freed from its surroundings over a considerable extent as in total parotidectomy.

Attempts at Prophylaxis in the Experimental Animal.—The total parotidectomy equivalent procedure produced paralysis sufficiently frequently to justify its use as a standard experimental procedure on which to test the possible prophylactic effect of a number of manœuvres. The general method used was to apply for 5 minutes to the facial nerve on one side after it was exposed superficially a solution of the agent to be tested, and then to free the nerve on its deep surface. As a control, in many of the experiments the same procedure was carried out on the opposite side, but using saline. The solutions tested were hydrocortisone succinate 5 per cent, histamine 0·1 per cent, and heparin 1000 units per ml. In addition, a variety of cooling manœuvres were used by applying ice to the operation area at different stages of the operation. The results can be summarized briefly since they were all substantially negative. Thus, with hydrocortisone there were 5 paralyses in 5 experiments, with histamine 6 paralyses in 8 experiments, and with heparin 4 paralyses in 8 experiments. In the various cooling experiments paralysis occurred in 14 out of 18 experiments.

The Time of Development and Duration of Paralysis.—The animals were examined for paralysis as a routine immediately after each operating session and the day following operation, and thereafter at varying intervals. Sometimes it was not possible to determine with certainty immediately after the operating session whether paralysis was present or not owing to the continuing influence of the anæsthetic. But the pattern of response was clear. If the animal was going to develop paralysis, such paralysis was present at the first examination after operation at which a decision on the point was possible. There were only two exceptions to this rule. Two rabbits, one on both sides, had paralysis the day after operation after we had felt certain that the eyelids were contracting briskly at the end of the operating session.

Complete recovery from paralysis had usually taken place by 2, 3, or 4 weeks after operation. In a very few animals recovery did not take place until 5 or 6 weeks after operation.

Response to Electric Stimulation, and Histological Investigations.—In 79 experiments the response to stimulation of the facial nerve at the end of the operative procedure was noted. In all 79, if the nerve was stimulated in the peripheral part of the field of operation where it was dividing into its fine terminal branches, muscular contraction always took place. If, however, the trunk of the nerve was stimulated, the response varied. In 37 there was no response or a poor response, and all had paralysis after operation. In 42 there was a normal response; of these 28 had paralysis after operation, and 14 no paralysis. The two animals noted above as developing a delayed paralysis both fell into this group and showed a normal response at operation to electrical stimulation of the nerve-trunk.

Mr. R. P. Gould, of the Department of Anatomy, kindly carried out histological tests for axon degeneration by Marchi's method on 6 facial nerves from 3 rabbits showing facial paralysis. The animals were sacrificed and the nerves removed at 2, 8, and 16 days after operation. The examination was confined to the trunk and the two main branches of the nerve, and in none of the specimens was axon degeneration observed.

DISCUSSION

The Cause of the Paralysis.—Conclusions derived from experiments on the facial nerve of rabbits are not necessarily applicable to man. The parallelism, however, of the experimental total parotidectomy equivalent procedure and total parotidectomy in man in their liability to produce facial paralysis does justify the tentative hypothesis that the same causes are operating in both. Leaving aside irrigation with perchloride of mercury, which presumably has a direct toxic action on some part of the nerve, there would appear to be three main possible explanations of the functional facial paralysis following parotidectomy, acting either alone or in combination:—

1. Direct traumatic interruption of nerve axon conductivity.
2. Indirect interruption from the secondary effects of trauma, such as œdema and inflammation.
3. Anoxia the result of ischæmia.

Œdema as an explanation of paralysis is particularly associated with the facial nerve, since it is one of the standard explanations of Bell's palsy, and the theoretical basis for therapeutic decompression of the nerve in its course through the petrous bone. But the evidence against œdema being an important factor in the functional facial paralysis that follows parotidectomy is strong. Both in man and in the animal experiments, if paralysis occurs, it is, as already noted, usually fully developed as soon as the subject has recovered from the effects of the anæsthetic, whereas one would expect the paralysis from œdema to be a gradually developing process. The failure of hydrocortisone to protect against paralysis in the experimental animals is also evidence against the importance of œdema. The causative influence of œdema cannot, however, be entirely dismissed. As already noted, there were rare examples of delayed paralysis in the experimental animals, and Janes (1957) has noted a similar phenomenon following parotidectomy in man, though we have been inclined to attribute any apparent worsening of paralysis that we have seen in the early hours following parotidectomy more to passive limitation of facial movements from diffuse traumatic œdema of the soft tissues. On the whole the influence of œdema as a cause of functional facial paralysis following parotidectomy is probably a small one.

The fact that experimentally the trunk and main branches of the facial nerve were remarkably resistant to gross trauma is strong evidence against direct

traumatic interruption of nerve axon conductivity being an important factor, especially since clinically one takes special precautions not to injure the nerve—for example, never picking it up with an instrument. There is, however, one traumatic factor which may be important, and that is longitudinal stretching of the nerve, a clinical example of which in gross form we have already noted. Both in total parotidectomy in man and in the equivalent experimental procedure, one introduces an instrument underneath the nerve to separate it from its bed. In the finer branches in particular, there must even with the greatest gentleness be some danger of stretching, especially at the point at which the branch is still fixed. We were unable to devise experiments to distinguish this form of possible interruption of the conductivity of the facial nerve from that due to ischæmia from stripping of the nerve.

Ischæmic anoxia is a well-established cause of interruption of nerve conductivity both in man (Lewis, Pickering, and Rothschild, 1931) and in animals (Denny-Brown and Brenner, 1944; Causey, 1955). The facial nerve, like other nerves, derives its blood-supply from the tissues through which it runs, and total parotidectomy in particular must cut off the blood-supply extensively owing to the freeing of the facial nerve from the stylomastoid foramen to the neighbourhood of the terminal branches. Owing to free intraneural longitudinal vascular anastomoses and their small metabolic requirements, nerves will tolerate considerable interference with their vascular supply without interference with their conductivity, but a limit is eventually reached (Causey, 1955). In favour of an ischæmic factor is the rapid recovery from the minor degrees of paralysis. The more prolonged interval before recovery of the major degrees of paralysis is easily explicable on the basis of marked and prolonged ischæmia leading to axon degeneration. We think it probable that ischæmia is the main factor in the functional paralysis following parotidectomy, and minor stretching of the smaller branches of the nerve an alternative or additional factor.

If ischæmia is the main factor, the question arises of the exact mechanism of its production. Is it due entirely to the anatomical cutting off of the blood-supply to the nerve from the surrounding tissues during freeing of the nerve, or do additional factors such as spasm or thrombosis play a part? In 24 clinical parotidectomies we kept the facial nerve moistened with a 4 per cent solution of papaverine sulphate during the course of the operation. In spite of this we had 2 examples of Grade III paralysis. This is evidence against vascular spasm being an important factor. We have already mentioned the substantially negative results with heparin as an attempted prophylactic against paralysis in the animal experiments, though the criticism might be made that we ought to have used it as an intravascular injection rather than as a local application. With this proviso, the evidence would by exclusion seem to suggest that the main mechanism of the ischæmia is anatomical. If this is so, the special susceptibility of the submandibular branch of the facial nerve presumably depends on a special precariousness of blood-supply, but as far as we are aware no detailed information exists on the comparative blood-supply of the various branches of the facial nerve.

Prevention.—The question of the prevention of functional facial paralysis after parotidectomy needs to be considered in proper perspective. Surgery of the parotid is performed to rid the patient of his disease. At times, even the complete sacrifice of the facial nerve and permanent facial paralysis may be a small price to pay for the attainment of this objective. Still less should fear of producing a temporary facial paralysis inhibit the surgeon in carrying out whatever operation is indicated on pathological grounds. Facial paralysis is, however, an unpleasant disability even if only temporary, and its avoidance is desirable if this can be achieved without prejudice to the success of the operation.

If the main cause of the paralysis is anatomical interruption of the blood-supply of the facial nerve, prevention must depend largely on the avoidance of any such interruption not necessary to the success of the operation. The blood-supply to the nerve is interfered with most in total parotidectomy, in which there is extensive freeing of the nerve on all aspects, and if this operation is performed not as a routine but only when clearly indicated, the incidence of paralysis should be appreciably reduced. The pathological justification for this policy has been considered elsewhere (Patey and Thackray, 1958). With peripherally situated tumours, particularly in the lower pole of the parotid, it may be possible at times to perform a partial superfacial parotidectomy well wide of the disease, but leaving the other pole of the gland intact, and thus to avoid dissection of the smaller nerve branches in the unaffected part of the gland.

Apart from these questions of general policy, a study of the blood-supply of the facial nerve suggests certain other possibilities of prevention. Blunt (1954), in a detailed anatomical study of the blood-supply of the facial nerve, has described two vessels which constitute an important source of the blood-supply of the part of the nerve under consideration. The first comes off the stylomastoid artery as it loops into the stylomastoid foramen; the second comes off the stem artery of the stylomastoid artery just peripheral to the foramen. This stem artery then runs forwards below and parallel to the trunk of the facial nerve, and is usually identified during the course of a parotidectomy. If the trunk of the facial nerve and the stem artery are identified a little away from, rather than at, the stylomastoid foramen, there should be a reasonable chance of avoiding damage to these two vessels. Our present technique of parotidectomy is designed to test this hypothesis.

To conclude: no measure or group of measures is likely to abolish the risk of functional facial paralysis after parotidectomy, and the patient must be prepared to take this risk as a necessary and relatively small price for the benefits of the operation. By being aware of the problem, however, and of its nature, the surgeon may be able to reduce the incidence and degree of the paralysis.

SUMMARY

1. Following parotidectomy with preservation of the facial nerve in 95 consecutive patients, functional facial paralysis occurred which was classified as Grade II in 31 patients and Grade III in 13 patients.

2. Further analyses showed that the main predisposing factors were total, as opposed to superfacial, parotidectomy, and irrigation of the wound with perchloride of mercury.

3. Facial paralysis was produced in rabbits by procedures equivalent to the parotidectomies performed in man. The procedure equivalent to total parotidectomy in its effect on the facial nerve caused a high incidence of facial paralysis.

4. The most likely cause of functional paralysis following parotidectomy is ischæmic anoxia of the nerve as a result of anatomical interference with its blood-supply.

5. Irrigation of the wound after parotidectomy is certainly contra-indicated with perchloride of mercury and probably also with other chemotherapeutic agents.

6. Functional facial paralysis following parotidectomy cannot be avoided completely, but it may be possible to reduce its incidence and degree without prejudice to the pathological soundness of the operation by measures directed towards reducing the interference with the blood-supply of the facial nerve.

We wish to acknowledge our indebtedness to Professor Eric Neil for his help and advice in the experimental work.

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THE ROLE OF SPLENO-PULMONARY PARENCHYMATOUS ANASTOMOSIS IN THE REDUCTION OF PORTAL HYPERTENSION IN DOGS

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IN a previous paper Walker, Field, and Conen (1959) described the operation of spleno-pulmonary parenchymatous anastomosis and produced evidence of the establishment of vascular connexions between the spleen and the lung in dogs following this procedure. Further investigation has been undertaken to determine the value of the procedure in lowering portal pressure in dogs, and this presentation is an analysis of the observations recorded.

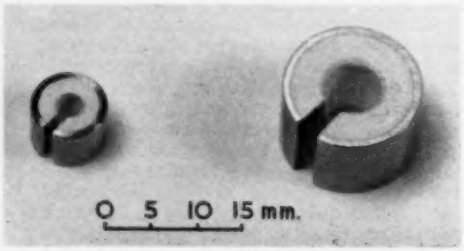

FIG. 512.—Small and large ameroids.

The difficulties of producing any lasting, severe portal hypertension in a dog have long been realized. Various methods have been utilized, including partial occlusion of the portal vein (Douglass, Mehn, Lounsbury, Swigert, and Tanturi, 1951), arterialization of the portal vein (Morris and Miller, 1951), production of hepatic cirrhosis with finely divided silica (Rousselot and Thompson, 1939), thoracic inferior vena cava obstruction (Volwiler, Bollman, and Grindlay, 1950), and others. All methods have serious limitations, such as inability to increase significantly the portal pressure, high mortality, only transient elevation of portal pressure, and, in the case of arteriovenous shunting, thrombosis of the shunt. Morris and Miller (1951) have concluded that "extrahepatic portal hypertension comparable to that seen in human subjects cannot be produced in the dog".

Despite these difficulties the present investigators determined to observe the effects of spleno-pulmonary parenchymatous anastomosis on dogs in which an attempt had been made to induce portal hypertension by the method described by Kerschner, Hooton, and Shearer (1946), which is outlined below.

THE EXPERIMENTAL METHODS

1. Operative Methods.—

Spleno-pulmonary Parenchymatous Anastomosis.—The technique of spleno-pulmonary parenchymatous anastomosis has been described in detail (Walker and others, 1959). Dogs weighing 8–20 kg. were used, and were anæsthetized with thiopentone and succinylcholine chloride. Antibiotics were used postoperatively.

Through a left thoraco-abdominal incision the spleen was delivered. A bulldog clamp was applied to the splenic pedicle, and the spleen prepared by excision of all but about $2 \times 1 \times 1$ cm. at the site of entry of the largest vessels.

A clamp was placed across the lower lobe of the left lung. An incision about 3 cm. long was made in the lung and continued deeply into its substance. After bringing the splenic pedicle up through the tendinous part of the diaphragm, the remnant of the spleen was inserted into the opening in the lung and the lung sewn over it. The diaphragm was closed around the splenic pedicle. The clamps were removed, an intercostal drain was inserted, and the wound was closed.

Induction of Portal Hypertension.—This was done in three stages along the lines suggested by Kerschner

and others (1946). After each stage at least four weeks elapsed before the performance of the subsequent stage.

At the first stage the abdomen was opened through a midline incision and the inferior vena cava displayed. The entry of both renal veins into the vena cava was demonstrated. A large-sized ameroid (*Fig.* 512) was placed on the vena cava above the entry of the renal veins to produce about 70 per cent occlusion. An ameroid is a metallic ring lined by plastic which slowly swells to increase the degree of occlusion in the post-operative period. The main value of its use in this experiment, however, lay in the ease with which the site of occlusion could be approached, at the time of the second stage, by feeling for the metal. In the first stage no attention was paid to whether or not the ameroid was placed above one or both of the middle suprarenal veins.

The second stage of this procedure consisted of re-opening the abdominal wound, dissecting down to the ameroid, and completing the occlusion of the inferior vena cava with a silk ligature. It was not considered necessary to divide the vena cava.

The third stage was conducted through a right anterior thoracic approach. The inferior vena cava was isolated, the right phrenic nerve was dissected from it, and a silk ligature was placed around the vein to produce approximately 70 per cent occlusion. Re-expansion of the lung was facilitated by the use of an intercostal drain connected to an underwater seal and a suction pump.

2. Investigation of the Dogs.—Numerous investigations were made on all animals in the series,

FIG. 514.—Venogram demonstrating spleno-pulmonary anastomosis. Radio-opaque dye has filled the splenic remnant, lung, parenchyma, inferior pulmonary vein, and the left side of the heart.

and as many are unrelated to the study of portal hypertension they are worthy only of mention. The observations are divisible into four groups:—

1. *The Changes in Portal Venous Pressure.*—Measurement of portal pressure was undertaken whenever the abdomen of a dog in the series was open. It was done by use of a water manometer filled with heparinized saline, and confirmed when possible with a Sanborn electro-manometer.

2. *The Presence and Degree of Ascites.*—This was assessed by frequent weighing of all dogs and recording the amount of fluid removed by paracentesis.

3. *Demonstration of Vascular Connexions between the Spleen and the Lung in Animals having a Spleno-pulmonary Parenchymatous Anastomosis.*—In each such animal an attempt was made to show the anastomosis by venography, neoprene latex injection, or histological techniques described elsewhere (Walker and others, 1959). In addition, in some dogs

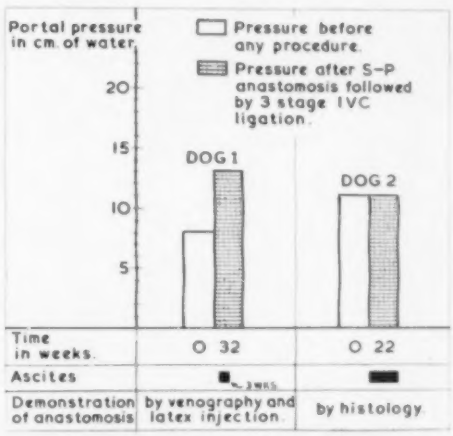

FIG. 513.—Results in Group A.

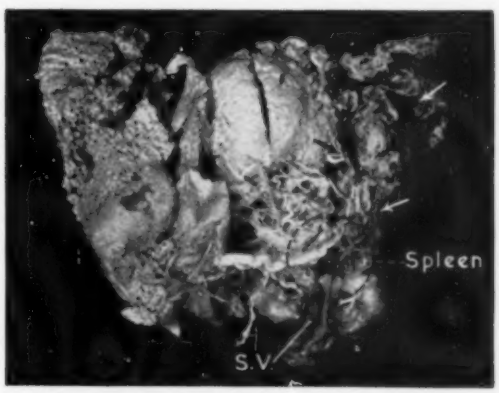

FIG. 515.—Latex-injected specimen of spleno-pulmonary anastomosis. The dark colour injected into the splenic vein has filled that vein (S.V.), the splenic remnant, and numerous vessels in the lung substance indicated by the arrows.

ciné-angiography and dye-dilution curve techniques were employed, but without very much success.

4. *Miscellaneous Tests* were conducted to show the general condition of all animals in the series. These included hæmoglobin, plasma-protein, and ascitic fluid protein estimations.

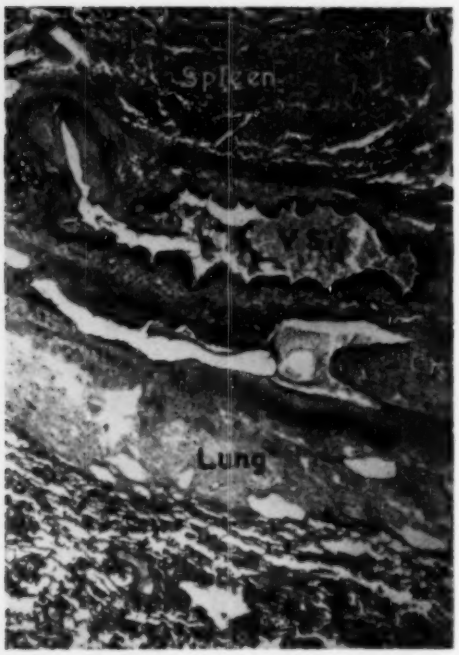

FIG. 516.—Histology of spleno-pulmonary anastomosis. The anastomotic area between lung and spleen contains numerous venous spaces (V.S.), many of which are filled with blood.

weeks later by the procedures outlined above to produce portal hypertension.

Group B.—The dogs in this group were subjected to the procedures used to produce portal hypertension. When these operations were completed, half of the survivors were retained as controls, and the other half were used further and constitute the next group.

Group C.—These dogs, half of the survivors from Group B, were subjected to spleno-pulmonary parenchymatous anastomosis.

THE EXPERIMENTAL RESULTS

These results are derived from observations on 10 dogs. Eight of them were selected for observation of the effect of spleno-pulmonary anastomosis on portal pressure and ascites. Two animals were kept for the same period of time as controls, and in these two portal hypertension was induced but no anastomosis was undertaken.

Results in Group A (Spleno-pulmonary parenchymatous anastomosis followed by three-stage inferior vena cava ligation).—The group consisted of 3 dogs. Dogs 1 and 2 failed to develop significant portal hypertension after the completion of all stages of inferior vena cava ligation (*Fig.* 513). The spleno-pulmonary anastomosis thus apparently protected these dogs from hypertension due to inferior vena cava ligation.

A functioning anastomosis was demonstrated by venography and neoprene latex injection in Dog 1 (*Figs.* 514, 515) and by sectioning serially with elastic tissue staining in Dog 2 (*Fig.* 516).

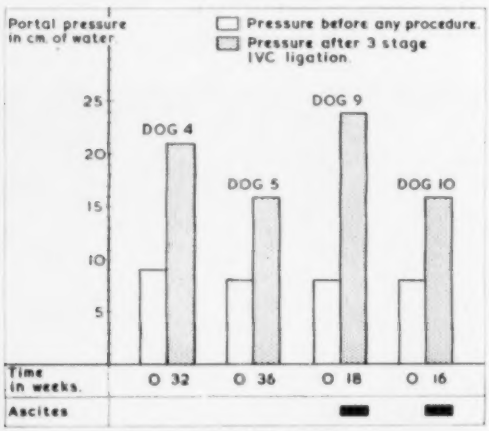

FIG. 517.—Results in Group B.

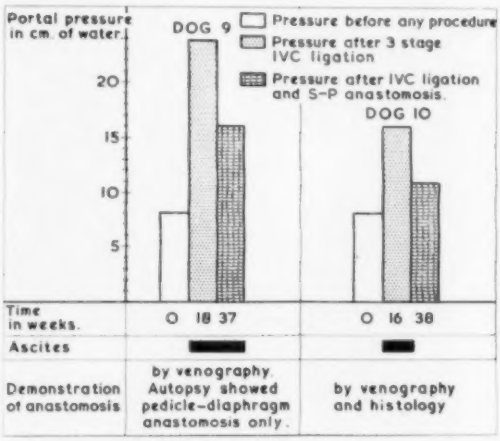

FIG. 518.—Results in Group C.

3. The Experimental Plan.—The effects of spleno-pulmonary parenchymatous anastomosis on dogs were studied both to protect them from developing portal hypertension and ascites and to relieve pre-induced mild hypertension and ascites. The dogs were treated in three different ways, and for the sake of convenience may be divided into Groups A, B, and C:—

Group A.—These had a spleno-pulmonary parenchymatous anastomosis followed not less than four

Dog 1 developed ascites 14 days after completion of inferior vena cava ligation. Three weeks later the ascites disappeared completely within a period of 2 days and did not recur for 22 weeks, at which time the dog was sacrificed. Dog 2 developed gross ascites and required paracentesis every 2 weeks till sacrificed 22 weeks later.

Dog 3 died of acute portal hypertension 2 days following the second stage of inferior vena cava ligation, and at autopsy no anastomosis existed

owing to a ligature having accidentally occluded the splenic pedicle. The spleen was necrotic. Death may have occurred because this dog was not protected by a functioning spleno-pulmonary anastomosis.

Results in Group B (Three-stage inferior vena cava ligation to produce portal hypertension).—This group consisted of 7 dogs, of which 3 (Dogs 6, 7, and 8) died post-operatively during the three stages of induction of portal hypertension. One of the three died from a post-operative pneumothorax (Dog 6) and the other two died from acute portal hypertension with massive bleeding into the lumen of the intestine (Dogs 7 and 8). The four survivors all developed mild portal hypertension ranging from 16 cm. to 24 cm. of water (*Fig.* 517).

Of the 4 survivors in this series, 2 were retained as controls (Dogs 4 and 5) and 2 were transferred to Group C (Dogs 9 and 10). The controls developed no ascites until sacrifice at 22 and 18 weeks, and at this time the portal pressures were 21 cm. and 16 cm. of water respectively. The two dogs transferred to Group C (Dogs 9 and 10) both developed ascites, and required repeated paracentesis.

11 cm. of water followed attempted spleno-pulmonary anastomosis (*Fig.* 518).

The procedure did not relieve the ascites in Dog 9 and it required paracentesis till sacrifice 18 weeks after anastomosis. At autopsy, the venous anastomosis

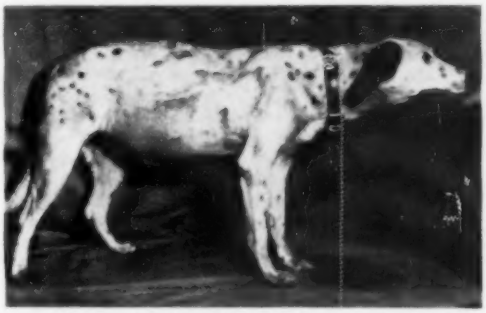

FIG. 519.—Experimental Dog 9 in Groups B and C. Shows the development of gross ascites, an umbilical hernia, and distended veins on the abdominal wall.

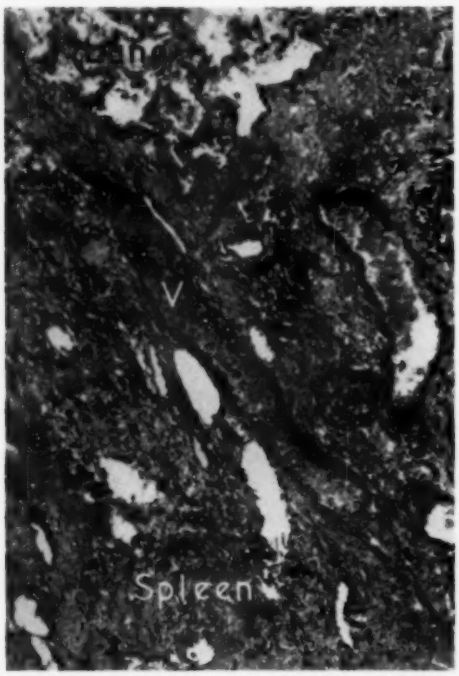

FIG. 520.—Histology of spleno-pulmonary anastomosis. The anastomotic area seen in one of serial sections of the specimen from Dog 10. Venous spaces, as the one shown (V), can be traced from the spleen into the lung.

FIG. 521.—Histology of spleno-pulmonary anastomosis. A highly magnified view of the venous spaces in the anastomotic area shows them to be lined by endothelium, and with no elastic tissue in their walls. Some spaces are filled with blood.

Results in Group C. (Inferior vena cava ligation followed by spleno-pulmonary anastomosis).—These two animals (Dogs 9 and 10) both developed a significant rise in portal pressure after vena cava ligation—24 cm. and 16 cm. of water respectively. In both, a reduction in this pressure to 16 cm. and proved to be inadequate (*Fig.* 519). Dog 10, having had frequent paracentesis up till the time of spleno-pulmonary anastomosis, did not require it again up to the time of sacrifice 16 weeks after anastomosis.

Venography in Dog 9 showed vascular communications between the splenic pedicle and the

diaphragm, pleura, and intercostal vessels. At autopsy, the spleen was found to be fibrous owing to compression of its pedicle at the site of entry into the lung. An anastomosis between the pedicle and the parietal pleura was confirmed by dissection.

A functioning spleno-pulmonary parenchymatous anastomosis was demonstrated in Dog 10 by venography and by histological techniques (*Figs.* 520, 521).

Spleno-pulmonary anastomosis reduced the portal pressure in Dog 10, and presumably the anastomosis around the splenic pedicle and diaphragm lowered the pressure in Dog 9.

Miscellaneous Observations.—Plasma-protein estimations and electrophoretic patterns did not show any gross abnormality in most dogs in the series. Hæmoglobin estimations gave results just a little below normal, none being less than 10·7 g. per 100 ml. blood, the normal in this laboratory averaging 14·7 g. per 100 ml.

Radiographs of the chest showed no significant abnormality. The dogs requiring repeated paracentesis became very thin, as was to be expected.

DISCUSSION AND CONCLUSIONS

In their former presentation on this subject (Walker and others, 1959) the authors stated that the effect of spleno-pulmonary parenchymatous anastomosis on mild portal hypertension in the dog would be investigated. The present series is the result of this endeavour. It is with a realization of the inadequacies of such a small series that the results are published, but this has been done for the reasons indicated below.

Kerschner and others (1946) described an attempt to produce portal hypertension in dogs using multiple-stage inferior vena cava ligation. Of 39 dogs used, only 4 dogs survived to the end of the experiment. The present investigators have confirmed that the procedures do produce mild portal hypertension in dogs, and have done so with a survival rate of 6 dogs out of the 10 dogs taken at the outset. This improved mortality may possibly be due to the use of an ameroid on the abdominal vena cava which permits the approach in the second stage of the procedure to be made with little dissection, and less likelihood of damage to the liver. Furthermore, early expansion of the lung by the use of a thoracic pump has reduced complications from pneumothorax in this laboratory.

The degree of portal hypertension achieved has never been great, and has varied from 16 cm. water to 24 cm. water. As in other series, there has been no evidence that œsophageal varices have been produced in the dogs. Three out of the four dogs that died did so from what appeared to be acute portal hypertension. In these dogs the mesentery showed large areas of hæmatoma, and the intestine contained a considerable amount of blood. Patchy acute ulceration was observed in the mucous membrane throughout the stomach and small intestine.

As in the experience of Kerschner, no obvious ascites was noted in less than 7 days after the third stage of the ligation procedures. In our 6 surviving dogs it was noted that ascites and portal hypertension seemed unrelated. Two dogs (Dogs 4 and 5) developed portal pressure of 21 cm. and 16 cm. water respectively, and neither of these dogs had ascites at any time. On the other hand, massive ascites occurred in one dog in which portal hypertension never developed (Dog 2).

The observations of the value of spleno-pulmonary anastomosis in portal hypertension in this series are obviously not statistically significant, but may be stated as impressions which should stimulate further investigation by different methods. It appears that spleno-pulmonary parenchymatous anastomosis done prior to attempted induction of portal hypertension may prevent the development of hypertension (Group A). In this group no significant elevation of portal pressure was produced in 2 dogs (*Fig.* 513). The third member died of acute portal hypertension and was found to lack a functioning anastomosis.

It was shown that spleno-pulmonary parenchymatous anastomosis in one dog, and an anastomosis between the splenic pedicle and the diaphragm in another, reduced mild portal hypertension to two-thirds of the values obtained by performing the procedures of Kerschner (Group C, *Fig.* 518). Two control dogs in which portal hypertension had been induced, and in which no anastomosis was performed, did not show such a reduction in pressure after the lapse of a similar period of time.

An Hypothesis concerning Parenchymatous Anastomosis.—While conducting the experiments just described, an hypothesis evolved which may be stated as follows: "Any two organs placed in apposition without a separating membrane will develop an intermingling of their circulations. The development of this anastomosis is dependent upon the character of the tissues, the area in contact, the pressure gradient, and the blood-flow requirement."

The concept of parenchymatous anastomosis is not new and has been the basis of many surgical procedures in the past, particularly pedicle skin-grafting and the following other examples: Key, Kergin, Martineau, and Leckey (1954) used pedicle grafts of jejunum to supplement the arterial supply to the myocardium. Removal both of the mucous membrane of the jejunum and of the epicardium was essential to prevent these structures from acting as a barrier to capillary outgrowth between the two tissues. These workers considered that the anastomosis obtained is through capillaries, and they felt that such a capillary anastomosis may have the carrying capacity of several large vessels. Subsequent coronary artery ligation proved the efficacy of the parenchymatous anastomosis by comparison of the low mortality-rate with the high rate in control dogs having no graft. These authors realized that one of the limitations of their experimental animal was the lack of requirement by a healthy myocardium for additional blood-supply.

In a similar type of experiment in which he attempted to augment the blood-supply to the heart by the use of pedicle skin-flaps, Neumann (Neumann, Braunwald, and Hinton (1956) and personal communication) likewise felt that increased flow of blood through the capillary anastomosis would only occur under conditions of increased demand. Such conditions are difficult to obtain in any experimental preparation.

Felder, Haglin, and Murphy (1956) coapted the decapsulated spleen and liver in rabbits and demonstrated a capillary anastomosis. Such anastomosis

prolonged life in rabbits after one-stage ligation of the portal vein in a controlled series.

Turunen and Laitinen (1959) described an application of the principles of parenchymatous anastomosis. They obtained an intrathoracic anastomosis between the spleen and the systemic veins in humans with portal hypertension and demonstrated the vascular connexions by splenoportography. They inferred that the greater the portal hypertension, the greater the degree of anastomosis, as they stated that "the abundance of collaterals was directly proportionate to the pre-operative severity of the varices".

In the present series of experiments parenchymatous anastomosis between the spleen and the lung has been utilized. Along with other workers, the present investigators have found the problem of inducing an adequate stimulus which will increase the capacity of a parenchymatous anastomosis a most perplexing one. The experience of earlier writers is sufficient to establish as fact part of the hypothesis stated above. This fact is that any two organs placed in apposition without any separating membrane or capsule will develop an intermingling of their circulations. The truth of the remainder of the hypothesis has been suspected by all authors, but has never been completely established owing to experimental difficulties. It may be that only experimental application to the human subject will prove that the capacity for increased blood-flow through a parenchymatous anastomosis is dependent on the character of the tissues, the area of contact, the pressure gradient, and the blood-flow requirements.

The Experimental Sequence.—The present investigation was undertaken in an attempt to find a solution to the problem of portal hypertension due to extrahepatic block in young children. Current methods utilizing venous anastomoses are unsatisfactory in these subjects as the anastomoses do not remain patent (Walker, 1959). A method was conceived which it was hoped would reduce the blood-flow through œsophageal and gastric varices by reducing the portal pressure. This was done by the establishment of a parenchymatous anastomosis between the spleen and some other suitable tissue.

Spleno-hepatic parenchymatous anastomosis was first used as a pilot experiment in an attempt to produce vascular connexions between organs. The idea that such connexions established in the thorax might prove more effective than an anastomosis in the abdomen led to investigation of the effects of splenic transposition to the thorax. Vascular connexions were successfully established between the intact spleen and the pleura. At the conclusion of this phase of the experimental work, the work of Turunen and Laitinen (1959) was published, which fortuitously provided, on clinical grounds, confirmation of our results obtained in a dog. Spleno-pulmonary anastomosis is considered to be a further advance. It provides an anastomosis which is situated in a more elastic location in which dilatation should be less confined by such rigid structures as the parietal pleura and the splenic capsule. In addition a more favourable pressure gradient probably exists. The superiority of intrathoracic anastomosis in the dog has been demonstrated in the present experiments, just as the operation used by Turunen and Laitinen (1959) appears to be more effective than earlier intra-abdominal procedures based on otherwise similar principles. The reasons for this superiority are not clearly understood, but it is suggested that they may be due to the intrathoracic negative pressure and the action of the 'respiratory pump'.

The series of experiments described in this paper was done in an attempt to investigate the role of spleno-pulmonary parenchymatous anastomosis in the relief of portal hypertension in dogs. Due to the limitations of the dog as an experimental animal, it has not proved possible to demonstrate adequately the value of the anastomosis in the reduction of portal pressure. Nevertheless, it is stressed that the impressions gained give every encouragement for further investigation, using a different approach, in the dog or a more suitable experimental animal. However, should more definite results not be forthcoming, it may be that spleno-pulmonary anastomosis should be given the crucial test in its application as a final resort in a moribund young child for whom present methods have nothing further to offer.

SUMMARY

1. A method of establishing parenchymatous anastomosis between the spleen and the lung in dogs is described, and the superiority of this method over other forms of parenchymatous anastomosis is stressed.

2. A series of dogs in which mild portal hypertension was induced is reported. The effects of spleno-pulmonary parenchymatous anastomosis in these animals were studied.

3. From the present investigation, and the work of others, the authors have evolved an hypothesis which states that the capacity for promotion of blood-flow through a parenchymatous anastomosis depends on the character of the tissues, the area of contact, the pressure gradient, and the blood-flow requirement.

4. Although the testing of the hypothesis has been undertaken in dogs, owing to the limitations of this animal as an experimental preparation it is emphasized that the conclusive proof may necessitate its investigation in a human subject, to whom no alternative can be offered.

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THE EFFECT OF DRUGS UPON EXPERIMENTAL PANCREATITIS IN THE RAT*

WITH SPECIAL REFERENCE TO BLOOD-AMYLASE LEVELS

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WHEN the pancreas is damaged by acute disease or injury, excessive amounts of pancreatic enzymes are released into the interstitial tissues. These seep into the peripancreatic area or are absorbed into the general circulation and are liable, under circumstances still ill defined, to produce further destruction of the pancreas and to have profound systemic effects.

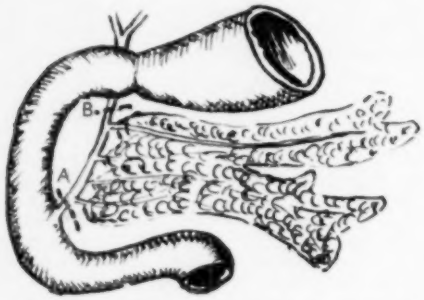

FIG. 522.—Diagram of the pancreas in the rat with multiple ducts entering a common biliary-pancreatic duct. Tie at **A** allows obstruction with continuity between biliary and pancreatic systems. Tie at **A** and **B** allows isolated obstruction to biliary and pancreatic duct systems.

Accordingly much of the treatment of acute pancreatitis has been directed towards the prevention of further tissue autolysis by depressing the secretion of the pancreas. Several of the drugs used clinically for this purpose have been reported as having a beneficial effect upon the course of the illness. In this paper is reported a study of the effects of five drugs on the normal rat and on the rat with induced obstructive pancreatitis, with special attention to alterations in pancreatic function as indicated by the amylase content of the blood.

METHODS

In most experimental work on pancreatitis it has been considered desirable to use for therapeutic trials an animal preparation with hæmorrhagic pancreatitis. Many techniques have been devised to produce experimental hæmorrhagic pancreatitis but all have the disadvantage that the methods of production are quite unnatural and the results obtained are too variable to allow anything except a crude comparison of mortality-rates between two large series of animals (Thal, 1954; Anderson, Von Hagen, Method, and Hehn, 1958). Moreover, in hæmorrhagic pancreatitis, whether naturally occurring or experimentally produced, many factors including blood-loss, infection, and electrolyte disturbances affect the course of the disease and may contribute materially towards a fatal outcome. It was decided in this investigation to use animals with simple œdematous 'pancreatitis' produced by duct ligation in which these other factors play a much less important part. This pancreatitis is in most instances a non-lethal lesion resembling histologically the interstitial pancreatitis occurring in man (Shingleton, Anlyan, and David, 1952).

1. Rat Preparations used.—These experiments were carried out on albino rats (Wistar strain) weighing between 250 and 350 g. Only male rats were used as the sexes have significantly different serum-amylase levels (Tuba and Wiberg, 1953). Throughout the experiments drinking water and food were unrestricted. In some animals the changes following duct ligation are more pronounced when the pancreas is at the same time stimulated to maximal secretion by food (Lium and Maddock, 1948), but this does not appear to be so in the rat (Block, Wakin, and Baggenstoss, 1954).

In the rat the pancreas is a diffuse structure located mainly in the mobile mesentery of the duodenum, with multiple pancreatic ducts entering into a common biliary-pancreatic duct (*Fig.* 522). These ducts are small, friable, and variable in number and position, so that effective obstruction to the pancreatic duct system requires ligation of the main biliary-pancreatic duct distally. When this is done, obstructive jaundice is inevitable and there is progressive distension of the obstructed ducts with rising mortality after the third day from rupture of these ducts. These rat preparations were therefore regarded as having a useful life of not more than four days and observations were limited to within this period. In the course of the experiments three preparations were used:—

Preparation A.—The common biliary-pancreatic duct was divided between ligatures at the duodenum. Obstruction was thus produced to both the biliary and the pancreatic duct systems with anatomical continuity between them so that regurgitation from one duct system to another remained possible.

Preparation B.—In this preparation a second ligature was placed around the common bile-duct below the junction of the hepatic ducts but above the level of entry of the pancreatic ducts. By this means isolated obstruction to the biliary and pancreatic duct systems was produced and no regurgitation of bile into the pancreatic ducts was possible.

Preparation C.—In a small series of rats the common bile-duct was ligated above the level of entry of the pancreatic ducts, producing obstruction to the biliary systems without pancreatic duct obstruction.

2. Biochemical Methods used.—The method used for the estimation of the serum amylase was

* This paper is based on work included in a thesis submitted to the University of Glasgow for a degree of Ch.M.

Talluto's (1954) modification of Somogyi's saccharogenic method (1938). For values below 3000 units/100 ml., a 1–10 dilution of serum in normal saline was used and for values above this level the test was repeated with a 1–100 dilution. To stabilize the *p*H of the test solution at these dilutions within the range of optimal enzyme activity, 2 ml. phosphate buffer (*p*H 7·0) was added, as recommended by Van Loon, Likins, and Seger (1952).

3. Collection of Blood Samples.—Adequate blood samples for serial estimations of amylase could not be obtained from these rats and only one measurement was made from each animal. At the appointed time therefore blood was withdrawn by direct cardiac puncture and the rat was then sacrificed and examined. Thus in each chart the results from all the rats used in a particular experiment have been plotted so that a composite picture is obtained. There is no direct measurement of the rise and fall of the serum amylase in any individual rat during the course of the experiment.

DRUGS INVESTIGATED

1. Cortisone.—In 1952 Stephenson, Pfeffer, and Saypol reported the successful treatment with cortisone of acute hæmorrhagic pancreatitis in a patient who was gravely ill and severely shocked. Since then there have been many reports of similar experiences (Hoste, 1953; Eskwith, Cacace, and Sollosy, 1955; Elman, 1955; Jones, 1955; Bloodworth and Cohen, 1955; Brockis and Jones, 1956; Rodgers, Meynell, Wilson, and Cooke, 1956; Kaplan, 1956). In some of these cases apparently responding to cortisone therapy, the fall in the serum amylase has been reported as being dramatic.

2. Ganglion-blocking Agents.—The vagus nerve when stimulated renders a pancreatic secretion rich in ferments (Pavlov, 1897), and therefore the chemical blockade of vagal impulses in acute pancreatic disorders is theoretically sound. The side-effects of atropine have precluded effective dosage, and several modern ganglion-blocking agents have been tried clinically in the hope that they might be more successful. Two such drugs, differing slightly in their mode of action, have been selected for the present investigation.—

a. Propantheline Bromide (*'Probanthine'*).—This drug has a strong anticholinergic action, being 2–4 times as active as atropine sulphate in producing neuro-effector blockade at the parasympathetic terminations. In large doses it also produces blockade of sympathetic and parasympathetic ganglia (Schwartz, Lehman, Ostrove, and Seibel. 1953).

b. Hyoscine N-butyl Bromide (*'Buscopan'*).—This is a quaternary ammonium compound which is said to have an almost specific effect upon the ganglia of the parasympathetic chain, with little or no effect upon the parasympathetic neuro-effectors.

3. Propyl-thiouracil.—Starr (1954, 1955) observed that thyroid therapy following operation encouraged the development of hæmorrhagic pancreatitis among other post-operative complications. He then used propyl-thiouracil in the treatment of pancreatitis, and formed the impression that adequate doses of propyl-thiouracil were of value in the early stages. Reid and his colleagues have studied the action of propyl-thiouracil in the laboratory. In dogs, large doses (300 mg.) lowered the serum amylase in most instances (Reid, Challis, Paulette, and Hinton, 1957); still larger doses (over 1000 mg. in 24 hours) reduced the incidence of induced hæmorrhagic pancreatitis (Paulette, Challis, Reid, and Hinton, 1958). From these and other studies (Reid and Kossa, 1954; Reid, Paulette, Challis, and Hinton, 1958) the opinion was formed that propyl-thiouracil as an anti-oxidative agent depressed synthesis within the pancreas so that cellular energy was diverted from secretory activity within the gland towards preservation of the integrity of the cell membrane with continued imprisonment of powerful proteolytic enzymes. In the view of Reid and his colleagues the enzymes with the greatest potential for tissue necrosis in acute pancreatitis were not the digestive enzymes but the intracellular degradative pancreatic enzymes. The use of propyl-thiouracil depressed the production of both the intracellular and the extracellular enzymes of the pancreas.

4. Acetazolamide ('Diamox').—Dreiling and Janowitz (1955) advocated the use of acetazolamide in acute pancreatitis on the grounds that "the escape of pancreatic enzymes in patients with acute pancreatitis may be due to increased hydrostatic pressure from hypersecretion of pancreatic juice against ductal obstruction". The bicarbonate in the pancreatic juice is produced within the pancreas by the action of carbonic anhydrase (Still, Bennett, and Scott, 1933). Acetazolamide inhibits the function of carbonic anhydrase and it has been found to be effective in reducing markedly the volume of pancreatic secretion in patients with pancreatic fistulæ (Hollander and Birnbaum, 1952; Watman, 1956; Papstrat and Miller, 1958).

EXPERIMENTS

Experiment 1: Normal Serum-amylase Levels in the Rat.—Serum-amylase levels were measured using the biochemical methods described above in 25 healthy rats receiving ample food and water. Readings ranged from 2290 units to 1504 units, with an arithmetic mean of 1810 units, standard deviation of 228 units, and a coefficient of variation of 12·6.

Experiment 2: Effect of Obstruction of the Biliary-pancreatic Duct Systems in the Rat.—In 45 rats the common biliary-pancreatic duct was tied between ligatures at the duodenum (Preparation A). At the intervals indicated on the charts, groups of rats were subjected to laparotomy, aspiration of cardiac blood, and biopsy of pancreas.

When the biliary-pancreatic ducts were tied, the rats became jaundiced, were listless, bedraggled, and dirty, and usually showed some abdominal distension. After 48 hours or so they improved in appearance and were more lively, although the urine remained heavily loaded with bile. By this time the pancreas, on laparotomy, was swollen and œdematous, with distension of the biliary and pancreatic ducts (*Fig.* 523). There was also a variable amount of intraperitoneal fat necrosis (*Fig.* 524), and usually some intestinal ileus. The blood taken by cardiac puncture was measured for amylase content. In *Fig.* 525 are plotted the serum-amylase values obtained (ordinate) and duration of duct obstruction (abscissa) for each of 27 rats sacrificed. The single circle at zero hours

represents the mean value on 25 normal rats as determined in the previous experiment.

Proximal and distal ligature of the biliary-pancreatic duct (Preparation B) was performed in 20 rats. There was no appreciable difference between these results and those obtained with Preparation A, whether measured by the degree of hyperamylasæmia,

FIG. 523.—Laparotomy in rat with common biliary-pancreatic duct isolated by proximal and distal ligatures (A, B). Marked distension of bile-duct above the proximal ligature.

histological changes in the pancreas, mortality-rates, or other means. This was true in the control series and the therapeutic trials, so that when parallel investigations with these two preparations were

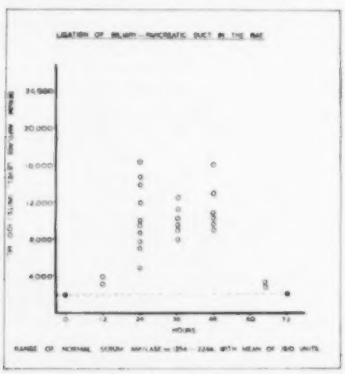

FIG. 525.—Serum-amylase levels obtained in 27 rats examined at the post-ligation time indicated on the abscissa.

carried out the separate sets of amylase readings have been charted (*Figs.* 525, 526, 531) but only the combined figures are analysed (*see Table II*).

Ligation of the biliary duct alone in 12 rats (Preparation C) had no significant effect upon the serum-amylase levels.

Discussion.—The rise in the serum amylase after ligation of the pancreatic duct is due not to any increased activity in the pancreas but to a greater absorption of the existing secretion into the blood-stream. In health the pancreatic enzyme secretion is for the most part exocrine, but a small and constant proportion is endocrine, i.e., into the blood-stream

FIG. 524.—Laparotomy in rat with common biliary-pancreatic duct ligated, showing intraperitoneal fat necrosis.

(Janowitz and Hollander, 1951). In acute pancreatic disorders the permeability of the pancreas is profoundly altered and the interstitial tissues of the gland are flooded with secretions which pass directly or indirectly into the blood. Intraduct secretion,

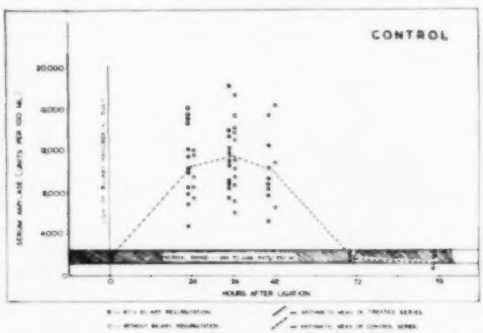

FIG. 526.—Control (untreated) rats. Serum-amylase readings in rats, using preparation A (dots) and preparation B (circles). Composite graph drawn from combined means at 24, 36, 48, 72, and 96 hours after ligation of the duct.

however, continues and in the presence of obstruction the pressure within the duct system rises until glandular secretion is brought to a standstill. The serum-amylase level then falls.

Experiment 3. Effects of Drugs upon the Serum Amylase in Normal Rats (*Table I*).—

RESULTS.—

1. *Cortisone.*—Cortisone acetate in dosage of 21·5 mg./kilo. body-wt./day was given subcutaneously to 21 rats. Groups of the rats were sacrificed after 5–12 days of treatment.

There was no difference between the behaviour of these rats and the controls, nor were any changes apparent at laparotomy. Serum-amylase values ranged between 1237 and 2872 units, with a mean of 2025 units and a standard deviation of 175 units.

2. *Ganglion-blocking Agents.*—

a. Propantheline bromide in dosage of 4·0 mg./kilo. body-wt./day was given intramuscularly twice daily to 6 rats. In this dosage there was no apparent upset or toxicity in the rats, but serum-amylase levels (1340 ± 208 units) were significantly lower than those found in control animals.

b. Hyoscine N-butyl bromide was given to 6 rats intramuscularly in dosage of 3·0 mg./kilo. body-wt./ day, in divided doses twice daily for 2 days. This dosage was well tolerated. As with propantheline bromide, serum-amylase levels (1135 units ± 207 units) were significantly lower than in the controls.

3. *Propyl-thiouracil.*—Propyl-thiouracil in suspension was fed to 6 rats by gastric tube in dosage of 100 mg./kilo. body-wt./day for 2 days. This dose is comparable to that found effective in dogs (Paulette and others, 1958). The behaviour of the rats did not appear to be greatly altered by this drug. Biochemical investigations showed that the serum-amylase levels (1358 units ± 203 units) were significantly lower than in the controls. Paper chromatograms after injections of tracer doses of I^{131} demonstrated that the intragastric propyl-thiouracil was effective in completely blocking thyroxine synthesis, particularly at the mono-iodo-tyrosine and di-iodo-tyrosine levels.

4. *Acetazolamide.*—Acetazolamide was given subcutaneously to 6 rats in dosage of 12·5 mg. b.d. (80 mg. acetazolamide/kilo. body-wt.), which is comparable to the dose stated by Janowitz (1958) to be the minimum effective dose in man. After 48 hours' treatment the animals were markedly acidotic, with a mean alkali reserve level 27 per cent below that found in untreated controls. Even with this dosage of acetazolamide, which was considered to be too toxic and subsequently was reduced to 60 mg./kilo. body-wt., there was no significant change in the serum-amylase levels (2013 units ± 164 units).

Discussion.—

1. *Cortisone.*—In these rat experiments, cortisone was given for a relatively short time (5–12 days). Serum-amylase levels, though in several cases slightly higher than the controls, were still within the normal range and statistically the differences were not significant.

Table I.—EFFECT OF DRUGS UPON SERUM AMYLASE IN NORMAL RATS

DRUGS	DOSAGE mg./kg. body-wt./day	SERUM-AMYLASE (units/100 ml.) MEAN ± S.D.	EFFECT
(Control)	—	1810 ± 228	—
Cortisone	12·5	2025 ± 175	Nil
Propantheline Bromide	4·0	1340 ± 208	Fall ($P < 0.01$)
Hyoscine *N*-Butyl Bromide	3·0	1135 ± 207	Fall ($P < 0.01$)
Propyl-thiouracil	100	1358 ± 203	Fall ($P < 0.01$)
Acetazolamide	60	2013 ± 164	Nil

Experiments in rabbits (Stumpf, Wilens, and Somoza, 1956) and studies in patients under steroid therapy (Rifkind, 1959) have indicated that cortisone given in the absence of pancreatic disease produces a rise rather than a fall in the amylase content of the blood. With prolonged cortisone therapy, pathological changes have been demonstrated in the pancreas similar to those of acute pancreatitis. This has been shown in man (Carone and Liebow, 1957) and in animals (Stumpf and others, 1956; Bencosme and Lazarus, 1956). A few cases of acute pancreatitis arising during cortisone therapy have been reported (Zion, Goldberg, and Suzman, 1955; Baar and Wolff, 1957; Marczynska-Robowska, 1957; Bourne and Dawson, 1958).

Thus it is possible that cortisone given over a long period predisposes to acute pancreatitis. At the same time there is no indication that a short course of cortisone given during the active destructive phase of severe acute pancreatitis to combat hypotension or overwhelming toxic effects would cause appreciable further destruction.

2. *Ganglion-blocking Agents.*—It has been shown that the ganglion-blocking agents, methantheline bromide ('Banthine') and propantheline bromide ('Probanthine'), are capable of reducing the amylase content and volume of the exocrine secretion of the pancreas both in man (Pfeffer and Hinton, 1956) and in the experimental animal (Annis and Hallenbeck, 1950; Thistlewaite, 1951). It would appear that vagotomy, whether surgical or chemical, has little effect upon the resting pancreatic secretion and that its inhibiting effect is marked only in the stimulated gland (Thomas and Crider, 1944; Pfeffer and Hinton, 1950; Routley, Mann, Bollman, Grindlay, and Flock, 1950; Shingleton, Fawcett, and Vetter, 1950; Thistlethwaite, 1951; Pfeffer, Stephenson, and Hinton, 1952; Dreiling, Drukerman, Hollander, 1952).

In these experiments the rats were given food and water freely, but the pancreas was not otherwise

stimulated to secretion. When propantheline bromide or hyoscine *N*-butyl bromide was given in full doses the serum-amylase levels were lower by 26 per cent and 37 per cent respectively than the mean level in

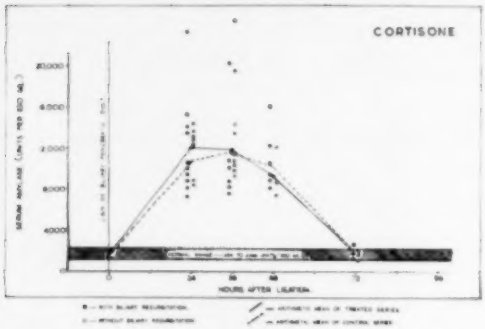

FIG. 527.—Serum-amylase levels obtained in rats treated with cortisone, compared with mean values obtained in controls.

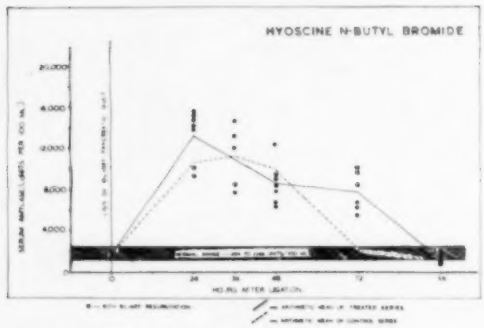

FIG. 529.—Serum-amylase levels obtained in rats treated with hyoscine *N*-butyl bromide, compared with mean values obtained in controls.

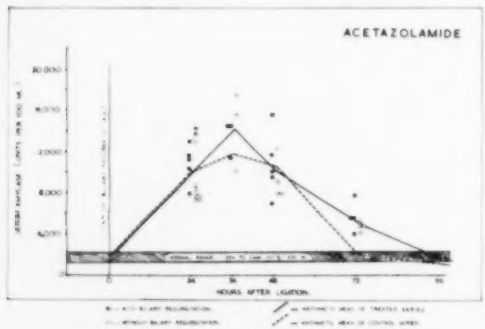

FIG. 531.—Serum-amylase levels obtained in rats treated with acetazolamide, compared with mean values obtained in controls.

untreated rats. No untoward toxic effects were noted with either of these drugs.

3. *Propyl-thiouracil.*—Rats fed with propyl-thiouracil had serum-amylase levels significantly lower than normal. This is in accord with the findings of Reid and others (1957) in dogs.

Propyl-thiouracil has an anti-oxidative effect upon all organs and tissues (Reid and Kossa, 1954).

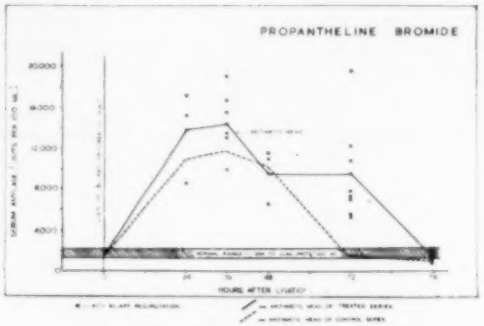

FIG. 528.—Serum-amylase levels obtained in rats treated with propantheline bromide, compared with mean values obtained in controls.

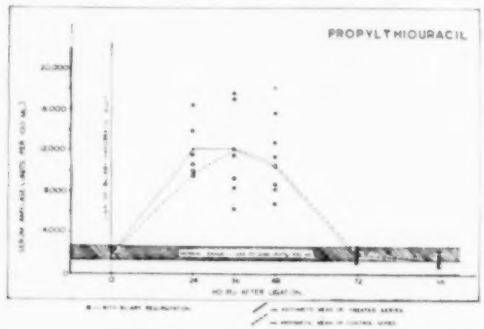

FIG. 530.—Serum-amylase levels obtained in rats treated with propyl-thiouracil, compared with mean values obtained in controls.

The radiochromatograms made during these experiments demonstrate the profound thyroid dysfunction present. Other harmful effects produced by propyl-thiouracil in rats are adrenal atrophy and inhibition of growth (Zarrow, Horger, and McCarthy, 1957).

4. *Acetazolamide.*—Acetazolamide in the massive dosage of 80 mg./kilo. body-wt./day had no effect upon the serum-amylase level in the normal rat. This result is in accord with the findings of Dreiling, Janowitz, and Halpern (1955) that acetazolamide had no direct effect upon the enzyme secretion of the pancreas.

Experiment 4. Effect of Drugs upon Induced Obstructive Pancreatitis in Rats.—The standard preparation used was Preparation A, in which the biliary-pancreatic duct was ligated at the duodenum only so that free communication remained between the biliary and the pancreatic duct systems. Dual experiments with both Preparations A and B were performed. The drugs were given from the time of operation and the dosage was as in Experiment 3, with the exception of acetazolamide, which was given in the reduced dosage of 60 mg./kilo. body-wt./day.

The serum-amylase results obtained are recorded in *Figs.* 527–531 and summarized in *Table II.*

RESULTS.—

1. *Cortisone.*—Complete investigations were carried out in 47 rats, of which 25 were Preparation A and 22 were Preparation B. Five other rats died prematurely, which approximates to the mortality-rate in the control group. No difference was observed between cortisone-treated animals and controls with respect to clinical course or histological appearances in the pancreas. At 24 and 36 hours after ligation, 4 out of the 32 cortisone-treated rats had serum-amylase values higher than had been observed in the controls. In view of the wide scatter in results, this finding has no statistical significance and serum-amylase values are essentially similar in both groups.

Table II.—EFFECT OF DRUGS UPON SERUM AMYLASE IN RATS WITH OBSTRUCTIVE PANCREATITIS

DRUGS	POST-LIGATION SERUM-AMYLASE (units/100 ml.) MEAN ± S.D.					RESULT
	24 hr.	36 hr.	48 hr.	72 hr.	96 hr.	
(Control)	10,700 ± 3196 (17)	11,615 ± 3250 (22)	10,300 ± 3490 (11)	1830 ± 572 (4)	1283 (3)	
Cortisone	12,000 ± 3987 (17)	12,000 ± 4982 (15)	9275 ± 1898 (9)	1882 ± 458 (6)	—	Nil
Propantheline Bromide	13,717 ± 4573 (3)	14,646 ± 3131 (6)	9664 ± 2728 (3)	9468 ± 4706 (8)	1560 ± 400 (6)	Raised at 72 hr. ($P<0.01$)
Hyoscine *N*-Butyl Bromide	13,343 ± 2500 (7)	11,269 ± 2938 (5)	8906 ± 1755 (7)	7938 ± 1958 (6)	1775 (4)	Raised at 72 hr. ($P<0.01$)
Propyl-thiouracil	12,080 ± 2533 (6)	11,666 ± 4701 (6)	10,600 ± 3420 (6)	2037 ± 329 (5)	1540 ± 320 (5)	Nil
Acetazolamide	10,010 ± 2207 (14)	13,886 ± 2847 (6)	10,100 ± 2470 (9)	5160 ± 1200 (8)	1773 (5)	Raised at 72 hr. ($P<0.01$)

No. of rats in each group in parenthesis.

2. *Ganglion-blocking Agents.*—

a. Propantheline bromide: Investigations were completed in 26 rats (Preparation A). Throughout the experiment the treated animals appeared more ill and lethargic than the controls. Laparotomy showed that the treated animals had more intestinal ileus but there was relatively less distension of the biliary and pancreatic ducts, and microscopically the development of acinar ectasia in the pancreas seemed slower. There was no difference between the two groups in the amount of fat necrosis in the peritoneum.

b. Hyoscine N-butyl bromide: Investigations were completed in 29 rats (Preparation A). Appearances were similar to those of rats treated with propantheline bromide, except that there was less intestinal ileus and less intraperitoneal fat necrosis. Measurement of the diameter of the dilated biliary-pancreatic ducts (*Table III*) and estimation of the amylase content of the secretion in these obstructed ducts (*Table IV*) showed that, compared with the untreated rats, the rate of intraductal secretion was reduced but there was no evidence that the drug had produced a reduction in the enzyme content alone. The effect of hyoscine *N*-butyl on amylase levels in the blood was not significantly different from that of propantheline bromide.

Table III.—DIAMETER OF BILIARY-PANCREATIC DUCT AFTER LIGATION (*Control and 'Buscopan' Series*)

POST-LIGATION INTERVAL (Hours)	MEAN DIAMETER B-P. DUCT (mm.)	
	Control	Buscopan
24	2·8	1·5
48	3·9	2·8
72	4·8	4·0
96	5·6	4·8

3. *Propyl-thiouracil.*—Investigations were completed in 28 rats (Preparation A). Five out of 33 rats died prematurely, but tube-feeding, with its increase in trauma, may have contributed to this slight increase in mortality-rate. The rats did not tolerate this drug well and appeared more ill than those in the previous groups. No differences were apparent on laparotomy and serum-amylase levels were all within the control range.

Table IV.—AMYLASE CONTENT OF RETAINED SECRETIONS AFTER BILIARY-PANCREATIC DUCT OBSTRUCTION (*Control and 'Buscopan' Series*)

DURATION OF DUCT LIGATION (Hours)	AMYLASE CONTENT (IODOMETRIC UNITS/100 ml.)	
	Controls	Buscopan
24	400,000 200,000 200,000	266,000
48	66,000 73,000 80,000	80,000 100,000
72	160,000 183,000	106,000 106,000

4. *Acetazolamide.*—It was not known what effect acetazolamide might have upon biliary secretion, so both rat Preparations A and B were used. Out of 58 rats operated upon, 16 (38 per cent) died prematurely, 9 of these within the first 48 hours after operation. This mortality-rate is considerably in excess of the wastage (about 10 per cent) occurring in the previous experiments. Compared with those

operated upon in the other series of experiments, the rats were even more toxic and ill and their belly-fur was continually sodden with the constant diuresis. Compared with the controls, no significant differences were apparent in the intra-abdominal appearances or in the microscopic changes in the pancreas.

The serum-amylase levels at 72 hours after operation were significantly higher than in the control series, though less than those obtained at 72 hours when either of the ganglion-blocking drugs had been used. This was true with both the rat preparations used, so that the presence of biliary reflux into the pancreas had no significant effect. The serum-amylase results at 24, 36, and 48 hours after duct ligation were all within the control range.

Discussion.—

1. *Cortisone.*—Large doses of cortisone have been given by Stewart, Elliot, and Zollinger (1959) to dogs with induced hæmorrhagic pancreatitis. They believed that the mortality-rate was reduced thereby and that cortisone had reduced the initial inflammatory reaction, since dogs dying in the early stages of the pancreatitis had less pancreatic œdema and inflammation and less ascitic exudate than untreated dogs.

In these rats with obstructive pancreatitis cortisone had no apparent effect upon the serum-amylase level, the clinical progress, or the pathological changes produced in the pancreas. There was therefore no obtainable evidence to support the view that cortisone, by reducing enzyme action within the pancreas, may help in the treatment of pancreatitis in man. The preparation used, however, does not permit consideration of any anti-inflammatory or anti-shock effect that cortisone may have upon the course of acute hæmorrhagic pancreatitis.

2. *Ganglion-blocking Agents.*—Several investigations have been made into the role that parasympathetic blockade might play in the treatment of acute pancreatitis by comparing the response to induced pancreatitis in vagotomized and non-vagotomized dogs (Kusunoki, 1936; Ripstein and Thompson, 1950; Schaffarzick, Ferran, and McCleery, 1951; Khedroo, 1957). Results appear to conflict: for example, Schaffarzick and his colleagues found that vagotomy resulted in a slower rise in the serum amylase in the first 24 hours and a reduced mortality-rate; whereas Khedroo found that vagotomy had no effect upon the course of experimental pancreatitis as measured by degree of hyperamylasæmia, histological changes in the pancreas, and crude mortality-rate. Much of the disparity in these results is due to the differing techniques used to produce pancreatitis. Vagotomy was much more effective, as indeed would be expected, when the obstructed pancreas was stimulated as by forced feeding (Schaffarzick and others) than when the gland was not stimulated but damaged by injection of a bile-trypsin mixture (Khedroo). Somewhat similar patterns of response have been observed by Shingleton and others (1952) in dogs with experimental pancreatitis treated with the parasympatholytic drug 'Banthine'. In dogs with œdematous pancreatitis produced by ligation of the pancreatic ducts and daily intramuscular injection of pilocarpine and secretin, the serum-amylase level after 48 hours was nearly 75 per cent lower in treated animals compared with untreated ones. In dogs with hæmorrhagic pancreatitis produced by ligation of the ducts and retrograde injection of bile-trypsin mixture serum-amylase levels in treated animals after 48 hours were still very high, being about 25 per cent lower than the mean level in untreated animals.

In these rat experiments, whereas propantheline bromide and hyoscine *N*-butyl bromide were effective in reducing considerably the level of serum amylase in normal rats, this was not so in the presence of pancreatic obstruction. With both these drugs serum-amylase levels were as high as in the controls and high levels were still obtained after 72 hours, whereas by this time levels in the control animals were low. The presence of less duct distension and of less œdema and acinar ectasia in the gland in the treated rats was evidence that these drugs had reduced the secretory activity of the pancreas. The reduction of fat necrosis with hyoscine *N*-butyl bromide is further evidence of this and it would be reasonable to attribute the prolonged hyperamylasæmia to the resulting slower build-up of back-pressure in the ducts. The raised serum-amylase levels in the first 48 hours after biliary-pancreatic duct ligation are due not to increased secretion by the pancreas but to a disturbance in the endocrine–exocrine function. Small alterations in the serum-amylase level following upon modest reductions in the total pancreatic secretion are obscured by the greatly increased spill of enzymes into the blood-stream.

The only objective side-effect that was observed with the ganglion-blocking agents was the apparent increase in ileus with propantheline bromide. This drug in man produces a marked and prolonged inhibition of stomach and bowel motility (Roback and Beal, 1953). This complication was not observed with the hyoscine *N*-butyl bromide, possibly due to its selective action on the parasympathetic ganglia without any effect on the myoneural junctions. Pharmacological studies by Wick (1957) have shown that hyoscine *N*-butyl bromide counteracts pilocarpine-induced intestinal spasm but has little effect upon the spasm induced by acetylcholine, which has its main point of action at the nerve-endings. It would therefore be expected to have little effect upon normal muscle tone.

These ganglion-blocking agents partially inhibit pancreatic secretion, and in this connexion would have a restricted value in the treatment of acute pancreatic disease. Possible benefits from their antispasmodic action upon the sphincter of Oddi and the ducts have not been taken into consideration since in the preparations employed the pancreatic ducts were permanently ligated. It seems that hyoscine *N*-butyl bromide is the drug more effective in reducing pancreatic secretion in the rat and also the one with fewer side-effects.

3. *Propyl-thiouracil.*—In the rats with obstruction of the biliary-pancreatic ducts, propyl-thiouracil had no appreciable effect upon the extracellular enzymes of the pancreas as measured by serum-amylase levels or upon the histological changes in the pancreas. Paulette and others (1958) found that propyl-thiouracil delayed and limited the development of the acute hæmorrhagic pancreatitis which can be consistently produced in dogs by a closed duodenal loop technique described by Pfeffer, Stasior, and Hinton (1958). As

the rat preparation was a benign œdematous lesion of the pancreas, there was no measurement of the part propyl-thiouracil could play in preserving the integrity of the cells of the pancreas and thus restraining the destructive capacity of the intracellular enzymes.

4. *Acetazolamide.*—When rats with obstructed biliary-pancreatic ducts were given acetazolamide there was a reduced rate of secretion from the pancreas as shown by the continued elevation of the serum-amylase level 72 hours after the ducts had been tied. This reduction in volume of the pancreatic secretion, however, was insufficient to have any effect upon the serum-amylase levels during the earlier period of obstructive pancreatitis. The rats in this experiment also appeared more ill, were acidotic, and had a higher mortality-rate than in those either untreated or treated with other drugs.

There is evidence that carbonic anhydrase is more effective against the carbon dioxide transport functions of the erythrocyte and the renal cortex than upon pancreatic secretions (Milne, 1956). It would seem undesirable to introduce in clinical pancreatitis, where recovery may depend on the maintenance of fluid and electrolyte balance, a drug which alters so considerably the acid–base mechanism in the body.

CONCLUSIONS AND SUMMARY

The ability of drugs to suppress the enzyme secretion of the pancreas during experimentally induced pancreatitis has been studied. The drugs investigated are some of those at present advocated for clinical use in acute pancreatitis—namely, cortisone, propantheline bromide ('Probanthine'), hyoscine *N*-butyl bromide ('Buscopan'), propyl-thiouracil, and acetazolamide ('Diamox').

Amylase levels in the blood of treated and untreated rats were measured. Propantheline bromide, hyoscine *N*-butyl bromide, or propyl-thiouracil given to normal rats reduced the enzyme secretion of the pancreas, serum-amylase levels being significantly lower than normal. Neither cortisone nor acetazolamide had any effect upon the serum-amylase level in the normal animal.

Ligation of the biliary-pancreatic duct in the rat resulted in an obstructive pancreatitis histologically resembling acute interstitial pancreatitis in man. With this preparation serum-amylase levels in untreated animals showed a well-defined pattern. Between 24 and 48 hours after ligation of the duct, serum-amylase levels were high, being several times the normal level. After 48 hours the rising pressure within the obstructed ducts suppressed pancreatic secretion so that 72 hours afterwards hyperamylasæmia was no longer present.

The following effects were observed upon the serum-amylase levels in rats with obstructive pancreatitis. With the ganglion-blocking agents, propantheline bromide and hyoscine *N*-butyl bromide, and with the carbonic anhydrase inhibitor, acetazolamide, hyperamylasæmia persisted for about 24 hours longer than in the untreated rats. This is attributed to a slower rate of accumulation of secretion within the obstructed ducts, with a slower rise in the back-pressure upon the acini of the pancreas. Neither cortisone nor propyl-thiouracil produced this effect.

All the drugs employed, including those which produced a lower serum-amylase level in the normal rat and apparently reduced the rate of enzyme secretion into the obstructed pancreatic duct, were ineffective in reducing at all the high level of serum amylase found in the first 48 hours after biliary-pancreatic duct ligation. A possible explanation is that in acute functional disorders of the pancreas, factors determining the degree of gland permeability or rate of absorption of enzymes from the interstitial tissues into the blood-stream are likely to obscure any lesser changes in the blood-enzyme level which might result from a modest reduction of the total pancreatic secretion.

No evidence was forthcoming from these experiments that cortisone given over a short period of time has any effect upon pancreatic function.

Most of the drugs caused undesirable side-effects which would limit their value in clinical pancreatitis.

In conclusion, of the drugs studied cortisone alone had no effect upon pancreatic secretion. The others were able to produce a partial reduction in pancreatic secretion, and the most useful as far as could be judged from these experiments were the ganglion-blocking agents. It seems that hyoscine *N*-butyl bromide is the more effective in reducing pancreatic secretion in the rat and it seems superior also in that it produces fewer disturbing side-effects.

Acknowledgements.—I wish to thank Professor W. A. Mackey for his interest and encouragement; Mrs. M. Hartley for her assistance with the biochemistry; and Mr. W. E. Towler for the photographs. I am also grateful to Dr. E. M. McGirr, University Department of Medicine, for the radiochromatograms, and to Dr. R. A. Robb, Department of Mathematics, University of Glasgow, for his statistical advice. 'Probanthine' was donated by G. D. Searle & Co. Ltd., 'Buscopan' by Boehringer Products Division, Pfizer Ltd.

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SHORT NOTES OF RARE OR OBSCURE CASES

EROSION OF STOMACH AND HÆMATEMESIS DUE TO PANCREATITIS

BY JAMES M. MOORE
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IN acute pancreatitis perforations of the posterior wall of the stomach have been described by Murphy (1934) and a perforation of the anterior wall in a child of 3 years has been described by Gross (1939).

Gastric or duodenal ulceration with bleeding has been reported on a number of occasions as a rare complication of acute pancreatitis, e.g., by Gambill, Baggenstoss, VanPatter, and Power (1948), Paxton and Payne (1950), and Thal and Perry (1957).

However, in a search of the literature no case similar to that now reported has been traced.

CASE REPORT

The patient was a married woman, 20 years of age, of rather obese build. She was admitted on Feb. 28, 1959, complaining of abdominal pain, nausea, and vomiting, of one week's duration. Over the preceding year she had suffered some dyspepsia, but otherwise the history was not significant.

The following day she collapsed and required resuscitation with plasma and blood transfusion. From clinical and biochemical examination it was thought likely that acute pancreatitis was the cause, but, as there was some doubt, laparotomy was carried out on March 2.

AT OPERATION.—The presence of acute pancreatitis was confirmed, the whole organ being grossly swollen and indurated with fat necrosis within the abdomen. The gall-bladder and bile-ducts felt normal and accordingly the abdomen was closed.

The patient was given a course of penicillin and streptomycin and made a gradual recovery. Occasional vomiting persisted, but her general condition was satisfactory till March 23, when she had a severe recurrence of acute pancreatitis. There was some hæmaturia and spontaneous bruising (the prothrombin time was increased and a low prothrombin level due to liver-cell damage may have been

contributory). This second attack settled after intravenous fluids, etc.

Nausea and vomiting, however, continued, and in the following weeks fluid and electrolytes were given rectally to supplement what oral intake was possible between vomiting attacks.

Examination of the fæces did not suggest any pancreatic insufficiency and the serum lipase was normal. On occasions, however, the serum amylase would rise to about 50 Wohlgemuth units per ml. and a slight icteric tinge was present at times. Barium meal on May 18 showed no interference with the emptying of the stomach although there was evidence of external pressure on the distal curvature. There was no distension of bowel.

The patient was now emaciated and vomiting was still a feature. Laparotomy seemed to offer the only hope and was carried out on May 22.

SECOND OPERATION.—The stomach was grossly contracted and this time its posterior wall was adherent to the pancreas, which was still enlarged and thickened but no cysts were present. It was thought that sphincterotomy might conceivably be of benefit, but entering the common duct proved difficult because of dense matting of tissue. Withdrawal of an aspirating needle resulted in some bleeding; a few stitches were required to control it. In view of a sudden deterioration in the patient's condition the idea of sphincterotomy was abandoned and, as starvation was an obvious feature, a feeding jejunostomy was quickly performed.

Feeding by jejunostomy was never satisfactory as it stimulated diarrhœa and the jejunostomy tended to act as a fistula with leakage of bile. Her condition became weaker early in June and there was some bilious discharge from the laparotomy wound. On June 14 she suddenly collapsed following the passage of a large amount of blood-stained material per rectum. Despite blood transfusion, vitamins K and K_1, calcium gluconate, and numerous other measures, she died the same evening after vomiting altered blood.

POST-MORTEM EXAMINATION.—The stomach contained altered blood and there was an ulcerated area 4 cm. in diameter on its posterior wall near the greater curvature, through which there was communication with a cavity containing blood-clot, in the position of the pancreas (*Fig.* 532). It appeared that the ulcer had resulted from erosion by pancreatic secretion and approximately the middle third of the pancreas had sloughed away; the head and the tail were firm and nodular.

The common bile-duct and pancreatic duct had a common opening at the ampulla of Vater and there was no stenosis. There were a number of small mixed stones in the gall-bladder and one in the cystic duct, but the common and hepatic ducts were free of stones. There were three minute perforations in the wall of the common bile-duct, apparently the result of sloughing at the site of stitches, and diffuse changes of peritonitis.

Histological examination confirmed the presence of subacute pancreatitis and in the stomach extensive inflammatory reaction around the ulcer. There was moderate fatty degeneration of the liver.

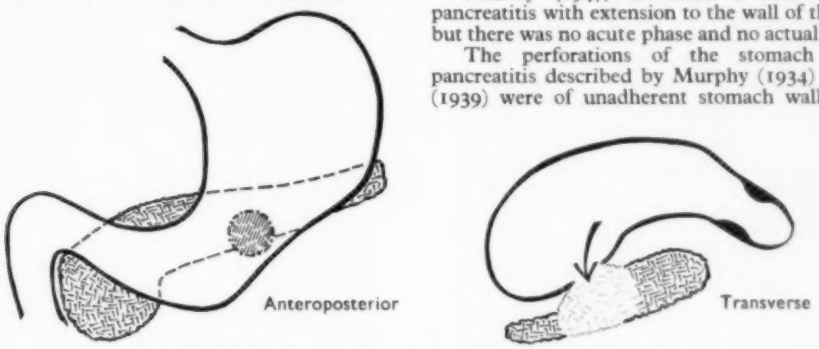

FIG. 532.—Diagram showing site of ulcer of posterior wall of stomach.

DISCUSSION

Mallory (1947) discussed a case of chronic pancreatitis with extension to the wall of the stomach but there was no acute phase and no actual ulceration.

The perforations of the stomach in acute pancreatitis described by Murphy (1934) and Gross (1939) were of unadherent stomach wall and were not produced by direct involvement from the pancreas.

Again, the gastroduodenal ulceration with bleeding reported by Gambill and others (1948), and others already mentioned, was not due to direct involvement. It has been suggested by Coffey (1952) that released trypsin might digest vessel walls (and certainly hæmaturia also may occur). Thal and Perry (1957) suggested that obstruction to biliary and pancreatic secretion might favour peptic ulcer formation.

In the present case the posterior wall of the stomach was presumably directly involved, leading to ulceration and perforation. This appears to have been the explanation of the continuing vomiting after the acute pancreatitis had settled.

SUMMARY

A case of recurrent acute pancreatitis is described in which vomiting persisted when the active phase had passed. Terminally there was hæmatemesis, and at autopsy it was found that the middle of the pancreas had sloughed away and the posterior wall of the stomach opposite had been eroded completely through.

I have pleasure in thanking Mr. J. P. Galloway for his guidance and permission to publish this case; and Dr. J. D. Barrie for the pathological and histological reports.

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SUPERIOR THYROID ARTERIOVENOUS ANEURYSM

By W. M. BEATTIE, J. B. OLDHAM, and J. A. ROSS, Liverpool

Arteriovenous aneurysm is well known as a result of trauma, but aneurysm between the superior thyroid artery and vein following ligature of the superior thyroid pedicle appears to be very unusual.

CASE REPORT

The patient, a man aged 25 years, was first seen in August, 1956, with classical signs and symptoms of primary thyrotoxicosis, which had been present for eighteen months. On account of the large size of the thyroid gland it was decided that surgery was the treatment of choice and a partial thyroidectomy was carried out (W. M. B.) on Sept. 4, 1956. The operation presented no difficulties and the superior thyroid pedicles were each ligatured with one ligature of No. 40 linen thread. Convalescence was uneventful and he returned to his work as a storeman in October, 1956. A further examination in January, 1957, revealed nothing abnormal and he was discharged.

He was seen again in March, 1958, because he complained of dizziness and 'black-outs', which had been present since December, 1957. He also mentioned the presence of a swelling in the left side of his neck, which he had first noticed in February, 1957, about five months after the operation. He said that the swelling had not enlarged appreciably since he first noticed it and that he was aware of a 'humming' in the region of the swelling at night, when he lay on his left side. Examination revealed a pulsating swelling, 12·5 cm. long by 2·5 cm. broad, in front of the left sternomastoid. A thrill was easily felt over the swelling and a loud systolic and diastolic bruit was heard. A diagnosis of arteriovenous aneurysm between the superior thyroid vessels was made, as it did not seem that a communication between two larger vessels could have occurred after a straightforward thyroidectomy.

Radiological visualization of the aneurysm was carried out (J. A. R.). After the administration of a test dose of diaginol (1 c.c. given intravenously) the patient was anæsthetized and a needle used for carotid angiography (Vim 2½ in. serum, short-bore) was inserted at a point above the left clavicle about 3·75 cm. distal to the aneurysm. The main difficulty was to decide on the timing of the exposure so as to obtain the best films showing the aneurysm. In order to overcome this difficulty it was decided to use a serial film changer, such as is used in aortography and angiocardiography. Ten c.c. of 50 per cent diaginol were injected rapidly while four films were exposed. It was then clear that the films taken early during injection were the most valuable and the injection was therefore repeated for exposure of a single lateral film at an early phase of injection. The arteriograms clearly show the superior thyroid artery entering the aneurysm, which is drained by a large vein into the internal jugular vein (*Figs.* 533, 534).

Fig. 533.—Anteroposterior angiogram showing aneurysm with the superior thyroid artery entering it and a large vein draining the sac into the internal jugular vein.

Fig. 534.—Lateral view of same.

Exploration of the neck was carried out (J. B. O.) on April 9 through a transverse incision. The sternomastoid was divided, exposing grossly enlarged common facial and internal jugular veins (*Fig.* 535). It was at first thought that the common facial vein was discharging arterial blood into the internal jugular vein, but further dissection revealed an aneurysm between the superior thyroid artery and vein in the region of the remnant of the left lobe of the thyroid gland (*Fig.* 536). The artery was ligated close to its origin and the aneurysmal sac was removed with ligature of the superior thyroid vein and common facial vein. The wound was closed around a rubber drain.

The patient's symptoms were immediately relieved, and he was perfectly well when last seen in July, 1958.

FIG. 535.—Gross distension of the common facial and internal jugular veins.

FIG. 536.—The aneurysm exposed by further dissection.

DISCUSSION

Cases of arteriovenous aneurysms following mass ligatures of arteries and veins together have been described in other parts of the body, but study of the literature reveals no example of superior thyroid arteriovenous aneurysm following ligature of the superior thyroid pedicle. The condition is mentioned by Lynn (Lynn, 1958; Martin, Lynn, Dible, and Aird, 1956) without elaboration as a complication of mass ligature of the superior thyroid pedicle.

Acknowledgement.—We wish to thank Mr. Lee of the Photographic Department, University of Liverpool, who kindly provided the photographs which were taken during the operation.

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SOLITARY NON-PARASITIC CYSTS OF THE LIVER

BY G. W. VAUSE GREIG AND R. STINSON, NEWRY

SOLITARY non-parasitic cysts of the liver are rare and it is difficult to estimate their exact incidence. Eliason and Smith (1944) found 28 examples in 20,000 successive post-mortem examinations, but only 2 ante-mortem cases in 211,046 admissions to hospital. Maingot in 1940 writes: "Up to the present date some 400 cases have been reported in the literature", but Manheimer in 1953 refers to 200 reported cases. He does stress, however, that this was not a "true measure of the incidence". This apparent discrepancy can be understood when the paper of Henson, Gray, and Dockerty (1956) is studied. They reviewed the Mayo Clinic records for the years 1907 to 1954 and there were 38 cases of solitary non-parasitic cysts of the liver treated surgically in this period. Of these, only 11 cases had symptoms attributable to the cyst and 1 other case had signs due to the cyst. Twenty-six of the 38 cysts were incidental findings at operation and the cysts in these cases were all small (less than 5 cm. in diameter). It can be assumed that many other cases were symptomless and, in the absence of a laparotomy, unrecognized. The 200 cases quoted by Manheimer (1953) are those cases treated because the cysts were causing symptoms or producing obvious signs. To this number may be added the 12 from the Mayo Clinic and approximately 10 cases reported since 1956 (Rizzo, 1957; Fores, Frauendorff, Ferrer, and Tambuatco, 1957; Bariety, Hepp, Gajdos, Coury, Thibault, and Ginsbourg, 1958; Warren and Polk, 1958).

Three further cases are reported. In 2 of these cases the symptoms can be attributed to the cyst. In the third case it is not possible to say whether the cyst produced symptoms, but it seems likely that some of the symptoms were due to the cyst. That 3 cases should be met in a single surgical unit during a period of four years suggests that they may be more common than is thought.

CASE REPORTS

Case 1.—

HISTORY.—Mrs. E. C., aged 65 years, complained of loss of appetite, nausea, and vomiting for three months.

There had been no severe pain, but a persistent ache in the epigastrium for the same period. She had lost 2 st. in weight. This patient had lived in the northern states of the U.S.A. for ten years, but had had no previous illness of note.

ON EXAMINATION.—A pale woman who had obviously lost weight. There was a big fixed mass in the epigastrium which moved on respiration and appeared to be continuous with the liver. This mass was not tender and her temperature was normal. A provisional diagnosis of carcinoma of the stomach with direct extension into the liver was made.

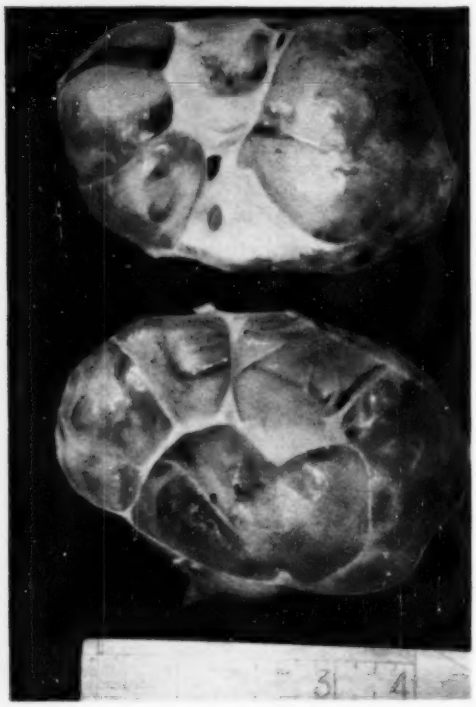

FIG. 537.—*Case* 2. Thin-walled cyst shows numerous trabeculæ.

AT OPERATION (Dec. 5, 1955).—The abdomen was opened by a right paramedian incision and further access was gained by a transrectus incision at right angles to the original incision. A huge mass (approximately 15 cm. in diameter) adherent to the anterior abdominal wall was encountered. In stripping it off the peritoneum the wall was breached and thick creamy material aspirated (subsequent culture was sterile). This revealed the extent of the cavity. It was bounded medially by the ligamentum teres and was extending deeply into the liver. The wall, in parts, was up to 1 cm. thick, but very friable. Separation from surrounding organs (stomach, duodenum, and transverse colon) was difficult, but the enucleation from the liver was comparatively easy, although an extensive raw area was left. Just behind this raw area was a rather thick-walled gall-bladder containing several stones. However, as the patient's general condition was giving cause for alarm, the gall-bladder was not removed. No other abnormality of the liver or other intra-abdominal organs was found. The raw area of the liver was covered with gelfoam and the wound closed around a drainage-tube.

HISTOLOGY (Dr. J. E. Morison).—"Portions of the wall of the abscess submitted to histology showed a non-specific chronic inflammatory reaction with nothing to suggest an amœbic infection or infection in a hydatid cyst."

PROGRESS.—Convalescence was uneventful. The drainage-tube was removed after five days and the patient returned home after seventeen days. There was intermittent discharge from the middle of the wound until May 30, 1956, when an unabsorbed suture was removed. Since then she has been completely symptom-free and has returned to her normal weight.

Comment.—Before operation this was thought to be a malignant mass; at first during the operation it was thought to be a huge mucocele of the gall-bladder; after operation it was thought that it was an amœbic abscess, an infected hydatid cyst, or a solitary metastatic abscess. However, the histology, the patient's subsequent excellent health, the relative ease with which the intrahepatic portion was shelled out, the absence of sepsis elsewhere, and our experiences of *Cases* 2 and 3 convince us that this was a solitary cyst of the liver which had become infected.

Case 2.—

HISTORY.—Mrs. S. R. was aged 30 years when first seen in March, 1955. She complained of pain in the right side of the abdomen which had, at first, been severe and referred to her right shoulder. Later it had eased and became a dull ache below the right costal margin. Her temperature had not been raised and she had not vomited. No abnormality was found on clinical examination. A cholecystogram showed a normally functioning gall-bladder with an indefinite filling defect which was thought to be due to a stone. As her symptoms rapidly cleared nothing further was done. She was seen again in December, 1956. Since her previous attendance at hospital she had been suffering from intermittent pain in the right side of the abdomen. This had never been very severe and was described as a "dragging ache". For one month the pain had been accompanied by repeated vomiting.

ON EXAMINATION.—There was a large soft mass in the right upper quadrant extending down to the level of the umbilicus. It was continuous with the liver and moved with respiration. It was tender on firm pressure. The pre-operative diagnosis was "mucocele of the gall-bladder due to solitary stone".

AT OPERATION (Dec. 17).—Through a right paramedian incision a large thin-walled cyst was removed from the right lobe of the liver. It was removed without rupture and was 12 cm. in diameter (*Fig.* 537). Approximately two-thirds of the cyst was intrahepatic and the gall-bladder was lying immediately behind the cyst. Enucleation of the cyst from the liver was easy. There was very little oozing from the raw areas and this was quickly controlled by diathermy and pressure. The gall-bladder appeared to be normal and no stones could be felt in it.

HISTOLOGY (Dr. J. E. Morison).—"The large cystic mass weighed 550 g. On section it was found to be a unilocular cyst traversed by numerous trabeculæ. It contained clear fluid. Histologically, the cyst wall is composed of fibrous tissue. It has been dissected very cleanly away from the liver and very little liver tissue is included. The lining of the cyst is in great part preserved and consists of flattened columnar or cuboidal cells. The cyst is a simple cyst and not a parasitic cyst."

PROGRESS.—The patient returned home on the tenth day and has been symptom-free since then.

Comment.—The initial severe pain in this case could have been due to hæmorrhage into a small cyst. Subsequent slow enlargement produced an easily palpable mass. The aching type of pain is typical.

Case 3.—

HISTORY.—Mrs. M. L., aged 60 years. For six months the patient had been complaining of an aching pain in the epigastrium, unrelated to food and worse after prolonged

standing. She was admitted to hospital with a typical attack of gall-stone colic, which rapidly settled, leaving some residual pain and tenderness in the right upper quadrant of the abdomen. She said that this residual pain differed from her previous epigastric pain.

On Examination.—A healthy female whose obesity made examination difficult. There was some tenderness on deep pressure below the right costal margin. Cholecystography showed a normally functioning gall-bladder containing two stones.

At Operation (Feb. 27, 1958).—Through a right paramedian incision a large cyst of the left lobe of the liver was easily shelled out. As in *Case* 2, there was very little bleeding except when a large artery was divided in the deepest part of the raw area. This was dealt with by a fine stitch. By the side of this artery was the opening of a bile-duct about 2 mm. in diameter. This was also closed with a suture. A thin-walled, normal looking gall-bladder containing two stones was removed.

Histology (Dr. J. E. Morison).—"The cyst weighed 125 g. and had a diameter of 8 cm. On section it is a thin-walled unilocular cyst showing some trabeculation of the lining. The content is clear serous fluid. Histologically, the cyst wall shows flattened cuboidal cells and some fibrous tissue elements. There is no inflammatory reaction. The cyst is a simple cyst. Though it has no communication with the biliary system it is almost certainly derived from the bile-ducts and, indeed, some dilated bile-ducts are present in the immediate neighbourhood."

Progress.—Returning home nine days after operation the patient has been symptom-free since.

Comment.—Although the acute attack of pain for which this patient was admitted to hospital was, almost certainly, due to cholelithiasis, it is thought that the aching pain in the epigastrium was due to the large cyst in the liver.

AETIOLOGY

The classification of solitary cysts of the liver which is generally accepted was put forward by Sonntag (1913): (1) Blood and degeneration cysts; (2) Dermoid cysts; (3) Lymphatic cysts; (4) Endothelial cysts; (5) Proliferative cysts; (6) Retention cysts.

Those in the first four categories are exceedingly rare and are easily recognized as separate entities on histological examination. Whether proliferative cysts (comparable to the cystadenoma of the ovary and, hence, true neoplasms) occur had been doubted, but the second case recorded by Warren and Polk (1958) is an example. However, the majority of solitary cysts are considered to be retention cysts.

Discussing the origin of retention cysts Warren and Polk (1958) suggest they come from: (1) Aberrant bile-ducts or blood-vessels; or (2) Obstruction of a bile-duct by inflammation. The original work of Moschowitz (1906) strongly supports the theory that solitary liver cysts arise from aberrant bile-ducts (or embryonal rests) as a result of congenital obstruction or inflammatory hyperplasia. The ease of enucleation of the cysts in *Cases* 2 and 3 above, the dilated bile-duct found at one point on the wall in *Case* 3, and the absence of signs of inflammation, incline us to the view that these cysts have arisen from aberrant bile-ducts.

CLINICAL FEATURES

Solitary cysts of the liver are usually very slow-growing unless hæmorrhage occurs into the cyst. Cases have been recorded in all decades of life, with a preponderance in women over middle age.

Symptoms.—Symptoms occur only when the cyst has reached considerable size unless there is a complicating factor. The commonest presenting symptom is pain. This may be an aching pain in the epigastrium or right upper quadrant of the abdomen caused by the drag of the weighty cyst on the ligaments of the liver, or due to expansion of the liver capsule. Sometimes there are short attacks of more severe pain due to bleeding into the cyst. Very rarely there may be severe pain accompanied by shock and collapse when a cyst ruptures or when a pedunculated cyst undergoes torsion.

Chronic inflammation, as in *Case* 1, produces persistent pain and tenderness. The other common symptom is a fullness of the upper abdomen or a palpable mass noticed by the patient. Because of the slow increase in size, pressure on neighbouring organs rarely causes trouble, but vomiting (as in *Case* 2) may result from pressure on the pylorus or duodenum. One of the cases reported by Henson, Gray, and Dockerty (1956) had gross liver failure, but this was probably due to associated vomiting and not due to destruction of liver tissue by the cyst. Another of their cases had a persistent sinus following previous surgical drainage.

Diagnosis.—Tumours of the liver, both primary and secondary, other abdominal cysts, carcinoma of the stomach, and gall-bladder disease are among the usual pre-operative diagnoses, and even at laparotomy symptoms should not be ascribed to a liver cyst unless careful examination excludes other lesions. An intermittent aching pain with a palpable mass to be felt in an otherwise healthy patient should, however, suggest the possibility of a cyst of the liver, but in most cases the diagnosis will not be made without an exploratory laparotomy.

TREATMENT

At laparotomy the presence of other, more serious, lesions must be excluded and surgical treatment is also contra-indicated if there are multiple cysts of the liver or associated cystic disease of the kidneys. Rupture, torsion, or infection of the cyst will, however, demand treatment even though congenital cystic disease is present.

Until recent years excision has only been attempted if the cyst had a pedicle or very little intrahepatic extension. Maingot (1940) suggested marsupialization if the cyst was largely intrahepatic, and Manheimer (1953) advised anastomosis of the cyst to stomach or a convenient loop of jejunum. Warren and Polk (1958) advocated excision or partial hepatectomy after identifying the biliary ducts. The ease of enucleation in all our cases and the smooth convalescence in the uncomplicated ones make us strongly support their view.

PROGNOSIS

Davis (1937), in a review of the literature to that date, gave the mortality as 22 per cent following operation. Recent advances in technique have lessened this considerably, and Henson, Gray, and Dockerty (1956) and Warren and Polk (1958) record small series without any operative deaths.

The true solitary cyst does not recur and removal will give complete cure.

PATHOLOGY

Large solitary liver cysts may occur in any part of the liver, the preponderance of the incidence in the right lobe being due to its greater bulk. In the series of Henson, Gray, and Dockerty (1956) the lining of the cysts (where recognizable) consisted of cuboidal epithelium in 75 per cent of cases. Columnar and squamous epithelium was also encountered. One of our cases showed cuboidal epithelium and the other both cuboidal and columnar. The change from the usual columnar epithelium of the bile-ductules to cuboidal epithelium is due to the tension in the expanding cyst.

SUMMARY

Three cases of large solitary non-parasitic cysts of the liver are reported. Although the total of previously reported cysts of this nature is small, it is suggested that they may be more frequently found if the condition is borne in mind. Aetiology and clinical features are discussed and treatment by enucleation advocated.

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TRANSPOSITION OF THE SCROTUM AND PENIS

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IN marsupials the penis is situated behind the scrotum. This relationship is very rare in man, and only 10 cases have been recorded. Two cases survived to adult life. One of these had no other associated defect and fathered one child (McGuire, 1954); the other,

FIG. 538.—Photograph showing the position and appearance of the penis.

with an unusually short penis and a web stretching between the penis and perineum, fathered four children (Appleby, 1923). A patient seen when eleven months old showed no other abnormality except a partially bifid scrotum (Campbell 1951). Hypospadias was present in 3 cases, as the only associated deformity in 2 cases (Bergman, 1911; Hontan, 1935), and accompanied by a partially bifid scrotum in 1 case (Forshall and Rickham, 1956). In the remaining 4 patients serious associated defects were discovered or suspected—1 case, with bilateral polycystic kidneys and the ureters opening ectopically into the bowel, survived only nineteen days (Huffman, 1951); 1 with a totally absent urinary tract survived only a few minutes (Francis, 1940); 1 suffered from an imperforate anus (Goss, 1953); and 1 was stillborn (Hinman, 1935).

CASE REPORT

An Indian baby was admitted to hospital three days after birth. He had been brought from an up-country station four hundred miles distant. The child had not passed urine since birth.

The scrotum was normal in appearance and contained two testicles. The penis was placed behind the scrotum and was considerably longer than normal (*Fig.* 538). The glans was completely exposed, the skin around it forming a loose collar. There was no evidence of any urethra, though the skin overlying the penis was quite normal. No distended bladder could be detected, and radio-opaque fluid injected into the rectum revealed no evidence of any communication between the bladder and rectum. The fæces did not appear to be mixed with urine. The left hand showed evidence of radial aplasia, the thumb being rudimentary and the first metacarpal absent.

The child survived for ten days without passing any urine, and then, without previous coma, died suddenly. An autopsy could not be obtained.

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A CASE OF PRIMARY MALIGNANT MELANOMA OF THE ŒSOPHAGUS

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PRIMARY malignant melanoma of the œsophagus is rare. One case, which occurred in the United Kingdom, was reported by Fleming and Van Der Merwe (1958). Previous cases have been described by Sirsat (1955), Fowler and D'Arcy Sutherland (1952), and Jaleski and Walds (1935).

CASE REPORT

A 67-year-old lady, under psychiatric treatment, developed dysphagia for solids, anorexia, lassitude, malaise, and loss of weight. She was referred for a barium swallow.

FIG. 539.—Tumour removed from œsophagus. The lower part is dark brown in colour; the upper part pale and fleshy.

During the examination she developed a severe circulatory collapse and was admitted to hospital for resuscitation.

ON EXAMINATION.—The patient was dehydrated, and showed evidence of weight-loss. There was no lymphadenopathy. The abdomen was scaphoid; the liver and spleen were not palpable. Numerous crepitations were heard on both sides of the chest. Pulse 100 per min. Blood-pressure was 50 mm. systolic. Hb 84 per cent = 12·3 g. per 100 ml. W.B.C.s 19,800 per c.mm., of which 74 per cent were polymorphs. Serum sodium and chloride were both reduced. Sputum culture grew *Staph. pyogenes*.

The barium swallow showed the following changes. The lower one-third of the œsophagus was markedly contracted, giving a 'rat-tail' appearance and allowing only a trickle of barium to flow through. Above this level the œsophagus was grossly dilated and irritable and showed numerous peristaltic waves. During the examination the patient vomited blood-stained material. The X-ray appearances suggested a carcinoma causing almost complete obstruction.

After preliminary resuscitation with intravenous fluids, cortisone, and antibiotics the patient was transferred to this hospital for further investigation. Despite therapy directed towards correction of dehydration, electrolyte imbalance, and collapse the patient developed a staphylococcal bronchopneumonia which did not respond to antibiotics and from which she died two days later.

POST-MORTEM FINDINGS.—The body was that of a thin, elderly female showing signs of weight-loss. No other significant external abnormalities were noted.

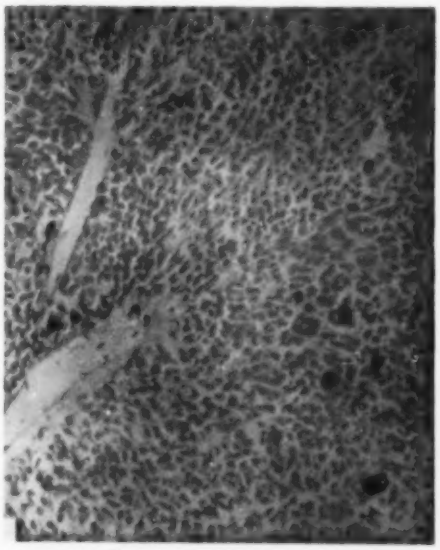

FIG. 540.—Photomicrograph of pale part of œsophageal melanoma, showing alveolar arrangement of cells and the presence of melanin. (× 133.)

A polypoid tumour mass occupied approximately two-thirds of the lumen of the œsophagus. It measured 17 cm. × 5 cm. × 4 cm. The tumour was lobulated and arose from a long broad anterior pedicle, the lower part of the tumour extending approximately 2 cm. below the pedicle. The lower part of the tumour was dark brown in colour, the upper part being pale and fleshy (*Fig.* 539). No macroscopic spread of malignant tissue through the wall was noted although some direct spread into the longitudinal muscle-fibres had occurred. At the time the tumour was thought to be a reticulosarcoma. The œsophagus stripped easily from the trachea. The lungs

showed an abscess-forming bronchopneumonia affecting the left lower lobe and a purulent tracheobronchitis.

One small secondary tumour 1·5 cm. in diameter was present in the right lobe of the liver. No other significant abnormalities were noted. The eyes were not removed, but vision had apparently been normal. Histologically, both the polypoid œsophageal tumour and the liver secondary were melanomata (*Fig.* 540). The cells, which were mainly irregularly oval and discrete, were arranged in an alveolar fashion in most parts of the tumour. Fine brown pigment was present in many of the cells in the darker part of the tumour, and some very marked accumulations of pigment were found in large round cells situated in and around the alveolar structure. A considerable amount of melanin was present in the loose subepithelial connective tissue of the œsophagus adjacent to the tumour pedicle.

We wish to thank Mr. A. M. Macarthur, Thoracic Surgeon, St. Helier Hospital, for allowing us to publish this case.

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RHEUMATOID NODULE OF THE CHEST WALL SIMULATING A TUMOUR

BY K. P. ROBINSON, LONDON

THE occurrence of a rheumatoid nodule of the chest wall is seldom observed on clinical examination or at autopsy even in those patients with rheumatoid disease in which nodules are widespread. It is therefore of interest that in the case to be described not only did a large nodule appear in the chest wall, but it resembled an intercostal tumour making its removal necessary.

CASE REPORT

Miss D. C., aged 64 years, developed rheumatoid arthritis at the age of 36 years, affecting at that time her hands but causing her little disability. Seven years later she had treatment with gold and hormones, but this produced little improvement although the disease did not progress until she was 46 years old, when her knees became involved. Some improvement resulted from physiotherapy at that time. At the age of 50 years she developed diabetes mellitus which required stabilization on soluble insulin and later maintenance on 10 units of protamine zinc insulin daily. She remained fit and well until three years ago when she lost weight and further joint involvement of the elbows and shoulders occurred. It was during her attendance at the Rheumatology Clinic that the symptomless chest-wall swelling was noted during examination of the shoulders.

ON EXAMINATION.—The patient was a thin elderly woman with rheumatoid arthritis involving the right temporomandibular joint, both shoulders, elbows, wrists, hands, and knees. A rheumatoid nodule was present on the right olecranon process. Three inches lateral to the spine of the second thoracic vertebra, on the left side, there was a firm mass, 3 cm. by 2·5 cm., deep to the trapezius and fixed to the second and third ribs. It was just visible when the shoulders were drawn forwards.

Chest radiography (*Fig.* 541) showed a lesion of the second and third ribs on the left posteriorly; in the affected area the ribs appeared to be indented and sclerotic for about 1 inch. Review of the earlier chest radiographs showed some erosion of the third rib three years previously, but a radiograph nine years previously showed no abnormality of the ribs. Radiographs of the hands, feet, shoulders, and knees showed the typical changes of rheumatoid arthritis.

The Wassermann and Kahn reactions were negative and the Rose-Waaler sensitized sheep-cell agglutination

FIG. 541.—Chest radiograph showing erosion and sclerosis of the left second and third ribs due to a rheumatoid nodule of the chest wall.

FIG. 542.—Margin of rheumatoid nodule showing spindle-shaped cells in palisade formation around a zone of fibrinoid necrosis. H. and E. (× 75.)

test was negative at a titre of 1/4. The erythrocyte sedimentation rate was 15 mm. in the first hour.

The diagnosis of rheumatoid nodule was considered but the unusual site caused this to be abandoned and a clinical diagnosis of neurofibroma was made.

OPERATION was performed by Mr. C. E. Drew on Nov. 5, 1959. Through a 7-in. incision medial to the inner border of the left scapula and sweeping around its lower angle the trapezius was divided and a firm tumour of trefoil outline exposed. This was situated on the second and third ribs and it extended into the muscles of the second intercostal space. The tumour could not be separated from the ribs by dissection and it was removed *en bloc* with 2 in. of the second rib and 3 in. of the third. The chest wall was closed in layers with catgut, the muscles being drawn together over the deficiency. An extrapleural drain was provided.

Examination of the excised specimen showed it to be a hard mass 3 cm. by 2·5 cm. attached to the second and third ribs extending into the intercostal muscles but not penetrating to the pleura. On cut section it was a white mass with a central punctate yellow appearance.

The patient made an uneventful recovery from the operation and was discharged home on the twelfth postoperative day.

HISTOLOGY.—The specimen (*Fig.* 542) was reported on as follows: Both fragments contain clefts lined by inflammatory exudate. One contains a large focus of fibrinoid necrosis around which spindle cells are radially disposed. Despite the site of this lesion the microscopic resemblance to rheumatic nodules is so strong that this diagnosis is suggested.

DISCUSSION

Subcutaneous nodules in rheumatoid disease are not uncommon; in 608 cases of rheumatoid arthritis reviewed by the committee of the American Rheumatism Association (1955) 26 per cent had nodules present. The aetiology of these nodules is unknown. Experimental attempts to induce them by subcutaneous injection of blood from and into rheumatoid subjects failed (Hart, 1943).

Collins (1957) described the characteristic histology of nodules in rheumatoid arthritis as follows:—

a. Proliferation of vascular and connective-tissue cells.

b. Local accumulations of lymphocytes, plasma cells, and leucocytes.

c. Necrosis.

d. Exudate, often rich in mucopolysaccharides that, with (*c*), gives rise to the picture of fibrinoid necrosis.

Occasionally there is a high lipoid content (Horwitz, 1949), as in one case where nodules were found on the scapula (Fletcher, 1945). Of patients with nodules in rheumatoid arthritis 78·1 per cent have a positive sensitized sheep-cell agglutination test (Ball, 1952).

Nodules are most frequently found subcutaneously along the ulna in the region of the olecranon and less often in the epicranial aponeurosis. Three cases with nodules in unusual sites (Mikkelson, Duff, Robinson, 1954) showed them in relation to the extensor pollicis longus and Achilles tendons, sclera, vocal cords, dura mater, lungs, spleen, and heart. One case with widespread nodules (Raven, Parkes Weber, Woodhouse Price, 1948) showed their presence in the scalp, elbows, wrists, anterior abdominal wall, and, at autopsy, also in the epiglottis, endocardium, pleura, pericardium, and spleen. Twenty-seven cases with rheumatoid nodules were reviewed (Kersley, Gibson, and Desmaris, 1945), but all the nodules were in usual sites and none in the chest wall.

Tumours of the chest wall have on several occasions been reviewed in detail (Zimminger, 1930; Hedblom, 1933; Speed, 1936; Janes, 1941; and Barrett, 1955). In none of these is there any record of a rheumatoid nodule occurring even in the differential diagnosis of chest wall tumours.

I would like to thank Mr. C. E. Drew and Dr. F. Dudley Hart for permission to publish this case; also Dr. A. W. Morgan for the pathological report and the photomicrograph.

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SURGICAL RESEARCH SOCIETY

THE thirteenth meeting of the Society was held at the London Hospital Medical College, London, on November 25 and 26, 1960, under the presidency of Mr. Hedley Atkins. The following papers were presented and discussed:—

1. H. B. TORRANCE, Manchester: "Radio-active Colloidal Clearance Technique to measure Liver Blood-flow in Man".

Since both colloidal P^{32} labelled chromium phosphate and heat-denatured I^{131} albumin are cleared selectively from the circulation by the liver in animals, hepatic blood-flow can be calculated if the clearance constant, the efficiency of clearance, and the blood volume are known. Work had been undertaken to elucidate in detail the application of this concept to the measurement of hepatic blood-flow in man.

1. Mean efficiency of liver clearance was 81 per cent.

2. Radio-activity of repeated blood samples yielded satisfactory results but the interpretation was complicated by multiple exponents.

3. Continuous recording of head radio-activity gave reasonably reproducible results, but also multiple exponents.

4. Continuous recording of liver activity was found to be the most convenient, reliable, and accurate method of determining the rate constant for I^{131} denatured albumin.

In 35 patients multiple simultaneous measurements had been made. The results provided a useful comparison of the four methods of measurement of liver blood-flow.

2. C. SHALDON (R. Milnes Walker), Bristol: "Adrenaline, Noradrenaline, and Portal Hypertension".

The adrenaline and noradrenaline content of portal vein plasma had been estimated (1) in 18 patients with portal hypertension who had undergone portocaval anastomosis, and (2) in 7 patients with normal portal circulations. After isolation by chromatography, the adrenaline had been estimated on the rat uterus preparation and the noradrenaline on the blood-pressure response of the pithed rat.

The catecholamine content in 72 per cent of the patients with portal hypertension was at least 10 times greater than normal. From these results and from the actions of adrenaline and noradrenaline on the portal pressure of man and the dog, it was concluded that adrenaline and noradrenaline played a role in the maintenance of portal hypertension in man.

3. H. D. RITCHIE, D. M. DAVIES, J. M. GODFREY, and R. G. S. JOHNS, The London Hospital: "Extracorporeal Methods for reducing High Blood-ammonia Levels".

Two extracorporeal methods had been used to obtain rapid reduction in the ammonia content of blood. With the Kolff twin-coil artificial kidney, reductions from 10 μg. per ml. of ammonia nitrogen in the blood to normal levels had been obtained after one passage through the coil. Ion-exchange resins offered a simpler alternative method. Data were presented on the relative effectiveness of some American and British resins in the removal of ammonia from blood and of the effect of linkage on ammonia uptake. When canine arterial blood, having a high ammonia content, was passed directly through an autoclaved column of resin and returned to a vein, significant reductions were obtained. Systemic and hæmatological sequelæ were minimal.

4. B. N. BROOKE, Birmingham: "The Liver in Ulcerative Colitis: An Interim Report".

Two concurrent studies had been undertaken, one histological, the other bacteriological, to assess the incidence and nature of hepatic changes in cases coming to operation and the incidence of portal bacteræmia. Liver biopsy had been undertaken in the last 51 cases and showed changes which were marked in 18, mild in 20, and insignificant in 13. Three features predominated: periportal infiltration with round cells, fatty degeneration, and cirrhosis (3 cases only). Second biopsies had been taken in 6 cases after treatment and these showed some repair of liver damage. From 24 of 90 consecutive cases organisms had been obtained from the portal blood. Half the cases who had developed jaundice had had infected portal blood. Plasma-proteins had been estimated in 41 cases. They were normal (albumin not less than 3·4 g. and globulin not more than 2·9 g. per 100 ml.) in 10; the albumin was low and the globulin high in 18; the albumin was low and the globulin normal in 5; and the albumin was normal and the globulin high in 8.

5. W. H. BAIN and M. GLOVER (W. A. Mackey), Royal Infirmary, Glasgow: "Assisted Circulation in Heart Failure".

An experimental preparation had been developed in the dog to assess the value of veno-arterial pumping in the relief of right heart strain and acute pulmonary hypertension. Acute right heart embarrassment had been caused by embolism of the pulmonary arterial tree. When the intracardiac pressures had become stabilized, partial heart/lung by-pass was instituted through a pump-oxygenator. This removed a proportion of the venous return, oxygenated it, and returned it to the arterial side of the circulation. The results showed a fall in right ventricular diastolic and mean pressures and pulmonary arterial pressure; reduction in right ventricular work and a rise in systemic pressure.

6. G. SMITH, D. LAWSON, S. RENFREW, R. SHARP, and I. LEDINGHAM, Western Infirmary, Glasgow: "The Beneficial Effects of Oxygen under Pressure in Acute Cerebral Ischæmia in Dogs".

The effects on electro-encephalographic tracings of 10 dogs with acute occlusion of the common carotid and vertebral arteries had been determined. Evidence of cortical ischæmia, while present in animals breathing air, did not appear when they breathed oxygen at a pressure of 2 atmospheres. The reasons for this protection were discussed.

7. M. F. A. WOODRUFF and S. SCHWARTZ, Edinburgh: "Heterotransplantation of Atherosclerotic Human Arteries after Endarterectomy".

Segments of human common iliac artery had been removed aseptically after death from elderly atherosclerotic subjects, endarterectomized, and transplanted heterologously to the dog aorta, 2 of them immediately, 2 after being frozen to $-79°$ C., and 2 after being freeze-dried. All were functionally satisfactory and aortography confirmed that they had remained patent. Some, but not all, of the grafts dilated. Two of the recipients were killed after 9 months and 11 months. The grafts did not show any trace of thrombosis; they had a smooth shiny lining, but histological examination did not show any definite endothelium. The other 4 dogs were alive and well after 15–17 months. Homografts of material prepared in this way might be of clinical value: aortic grafts carrying visceral branches might be used in the treatment of

hypertension of renal origin and of mesenteric arterial insufficiency.

8. P. J. FOLCA and W. T. IRVINE, The London Hospital: "Tissue Specific Activities following Injection of Tritiated Hexœstrol: Comparison with Results of Bilateral Adrenalectomy and Oöphorectomy for Advanced Breast Carcinoma".

The clinically-assessed response to bilateral adrenalectomy and oöphorectomy for advanced breast carcinoma had been compared with the specific activity of normal tissues and tumour tissue obtained at operation after the injection of 100 μg. of tritiated hexœstrol. Measurement of blood, fat, and, in later cases, fibrous tissue content of the specimens had been attempted by appropriate methods, and tissue tritium-specific activities, assayed by a gas-counting technique, had been corrected accordingly. In each patient the specific activity of tumour tissue had been related to uptake in rectus muscle at the same time. The tumour/rectus ratio was much higher in patients who responded to operation than in those who did not.

9. W. T. IRVINE and C. F. NOON, The London Hospital: "Isolated and Total Body Perfusions in the Treatment of Advanced Malignant Disease".

Twenty patients had been treated by the isolated perfusion technique and 4 patients by total body perfusion. Four different cytotoxic agents had been used: nitrogen mustard, melphalan, melphalan ester hydrochloride, and actinomycin D. The course of some of these tumours was affected by the drugs available; in particular, melanomata showed a response to melphalan. Some experimental studies in the use of cytotoxic agents in isolated limb perfusion in dogs were described.

10. D. H. L. EVANS and J. G. MURRAY, King's College Hospital: "Regeneration of Unmyelinated Nerve-fibres".

The abdominal vagus nerves in the rabbit and cat are composed of unmyelinated fibres; after a crush lesion at this level axons regenerated and function returned to the stomach in three to four months. In contrast, after a lesion of the cervical vagus, where there is a mixture of myelinated and unmyelinated fibres, function never returned to the stomach. Regenerating unmyelinated axons were diverted from their original pathway to the stomach and guided by myelinated fibres into the recurrent laryngeal, cardiac, and bronchial branches. This re-routing of regenerating unmyelinated by myelinated fibres appears to be a general phenomenon in the nervous system.

11. C. G. CLARKE, V. J. CURNOW, J. G. MURRAY, F. O. STEPHENS, and J. H. WYLLIE, King's College Hospital: "The Mechanism of Histamine-induced Gastric Secretion".

The augmented histamine test was found to provide a reproducible, maximal stimulus to gastric acid secretion in man. Impressive amounts of pepsin were also secreted, being about two-thirds of the amounts secreted in effective insulin tests. Acid outputs were equal in both types of test. Intramuscular hexamethonium bromide (25 mg.) or atropine sulphate (0·6 mg.) caused 50 per cent reduction in acid and pepsin secretion in both histamine and insulin tests. These results indicate that histamine: (1) stimulates pepsin as well as acid secretion; and (2) acts, at least in part, through nerves.

12. I. E. GILLESPIE, Sheffield: "The Effect of Vagotomy and of the Augmented Histamine Test on Pepsin Secretion in Man".

In 13 duodenal ulcer patients a reduction in basal pepsin output was demonstrated after surgical vagotomy. A wide variation in individual readings, and the difficulty of interpretation in the presence of low acid concentration, made the significance of this reduction doubtful. In 17 duodenal ulcer patients the augmented histamine test was found to bring about a threefold increase in the output of pepsin before and after vagotomy. An analysis of the results pointed to actual stimulation of pepsin secretion rather than 'wash-out' by acid. The increase in pepsin output in response to the augmented histamine test was about one-third that of the increase in acid output, and this ratio was undisturbed by vagotomy.

13. J. KYLE and F. STEPHENS, Aberdeen: "Gastric Acidity after Duodenal Ulcer Surgery".

Maximally stimulated gastric acid secretion had been measured before and after operation in 44 patients with duodenal ulceration to determine: (1) if the post-operative recovery of gastric juice could be increased and rendered more reliable by the use of a stomal blocking technique; and (2) which of three standard operations gave the greatest and most consistent reduction in acidity. The stomal blocking technique did not improve the recovery of gastric juice after either vagotomy plus antrectomy or Polya gastrectomy; after vagotomy plus gastro-enterostomy it gave high and misleading results. The technique is, therefore, unnecessary and undesirable in post-operative acidity studies. Polya gastrectomy was the most effective operation in reducing acidity.

14. N. C. R. W. REID, R. M. HACKETT, and R. B. WELBOURN, Belfast: "The Influence of Cortisone on the Parietal-cell Population of the Stomach".

Cortisone increases the 'maximal' acid secretory response of the stomach to histamine (Clarke, S. D., Neill, D. W., and Welbourn, R. B. 1960, *Gut*, **1**, 36). Experiments had been undertaken in dogs to discover whether this could be accounted for by an increase in the parietal-cell population. Cortisone had been injected intramuscularly and the stomachs removed. In each the area of the acid-secreting mucosa had been measured and representative sites examined microscopically. An average total dose of 28 mg. per kg. did not influence the area, but increased by 50 per cent the number of parietal cells per unit area of mucosal surface and the total parietal-cell population.

15. J. W. MCINTOSH, N. ANDERSON, H. L. DUTHIE, and A. P. M. FORREST, Western Infirmary, Glasgow: "The Effect of an Adrenal Cortical Inhibitor on Canine Gastric Secretion".

The effect of the adrenal inhibitor SU4885 on gastric secretion had been studied in dogs with separate pouches. Initially the drug had been given (1) by single intravenous injection during the secretory response to the ingestion of a meal of meat, subcutaneous mecothane, and subcutaneous histamine; (2) by continuous intravenous injection during the secretory response to histamine. No inhibition was noted. In four dogs SU4885 had been given orally for 7–15 days while 24-hour collections of juice were being made. When given in this way it reduced the secretion of acid.

16. H. L. DUTHIE, C. A. OWEN, and C. F. CODE, Western Infirmary, Glasgow, and Mayo Foundation: "Iron Absorption from the Small Bowel of the Dog".

17. A. G. COX (A. W. Kay), Sheffield: "A Possible Explanation of Failure of Radio-triolein to Diagnose Steatorrhœa".

In a clinical trial radio-iodinated triolein had failed to diagnose steatorrhœa in 18 of 33 cases with a high chemical fæcal fat excretion. A possible explanation was instability of the radio-iodine label in the alimentary tract. To

investigate this point, a method using an anion exchange resin had been evolved and applied *in vitro*. When incubated with duodenal juice, six batches of triolein, tagged with the standard I^{131} Cl label, showed a steady rise in the amount of the radio-isotope liberated. This demonstration of instability of the label requires *in vivo* study. The method also confirmed that the simple I^{131} label, still occasionally used, is highly unstable.

18. A. N. SMITH, D. H. FRIEDLANDER, and C. W. J. HUSTON, Edinburgh: "Absorption Studies in Ulcerative Colitis".

The absorption of sodium chloride from the colon of normal subjects and of patients with ulcerative colitis had been studied by the use of Na^{24} and Br^{82} as retention enemata. Differential movement of Na^{24} and Br^{82} from the colon was demonstrated by their appearance in blood samples. To measure their relative mass uptakes a correction had to be made for the effective body spaces and rates of movement of the ions into them. Chloride (Br) was much more readily absorbed than sodium. Patients with colitis absorbed excessive amounts of chloride (Br), with a much smaller alteration in sodium absorption, when presented with an artificial gradient of these ions. The changes were probably related to the local damage of the bowel or to its vascularity.

19. J. STEYN and T. BELL (H. Dudley), Aberdeen: "Viruses in Lymph-nodes of Children with Acute Abdominal Pain".

Many children admitted to hospital with a provisional diagnosis of acute appendicitis are subsequently found, either clinically or at laparotomy, to have enlarged mesenteric lymph-nodes and sometimes other evidence of lymphadenopathy. Furthermore, in acute intussusception the lymph-nodes are often enlarged. Using the plasma clot explant technique, adenoviruses of various types were isolated from lymph-nodes in 10 of 11 cases of intussusception and in 11 of 22 cases of acute mesenteric lymphadenitis. Positive cultures were obtained in only 1 control out of 23. These findings may be of considerable significance in the causation and diagnosis of acute abdominal symptoms in children.

20. W. F. P. GAMMIE, A. H. E. MARSHALL, and R. B. WHITE (V. W. Dix), The London Hospital: "The Role of Immunological Tests in the Surgery of Thyrotoxicosis".

Immunological studies had been made on sera from 230 patients with thyroid disease, including 130 with thyrotoxicosis. Among the latter, the complement-fixation test was negative in 86 and positive in 44. After subtotal thyroidectomy histological studies had been made and the patients followed up for over two years. Post-operative myxœdema occurred in 8 patients (8·8 per cent) with a negative C.F.T. and in 12 patients (27·3 per cent) with a positive C.F.T. There was an increased incidence of post-operative myxœdema among those cases showing serological and histological evidence of an immune response, and the need for a less radical surgical approach in these cases was discussed.

21. L. P. THOMAS, Cardiff: "Tolerance of Skin Homografts between Untreated Litter-mate Puppies".

Full-thickness 2 × 2 cm. skin homografts had been exchanged between 10-week-old litter mate puppies in 5 experiments. Tolerance was found in 2 instances: survival of the grafts with normal growth of brown hair on black-haired hosts was followed for 128+ days and 53+ days respectively. A 'second-set' 3 × 3 cm. homograft had been applied in 1 instance between the same donor and recipient and survival again demonstrated (for 43 days). The homograft from the black dog did not survive on the brown-haired recipient. It is presumed that the tolerance of these homografts was the result of mixing of placental blood and was similar to the condition existing in freemartin cattle described by Owen (*Science*, 1945, **102**, 400).

22. N. W. STRUTHERS (R. Shackman), Post-graduate Medical School: "Renal Pelvic Pressures in Dogs".

Renal pelvic pressures had been studied in dogs during natural secretion of urine and saline-induced diuresis, and after production of hydronephrosis by low ureterocolic anastomosis. The renal pelvic pressures had been measured through nephrostomy tubes and recorded by N.E.P. inductive transducers and carrier amplifiers. Results showed a low resting renal pressure which increased in linear relationship to the secretion of urine during diuresis. An intrinsic cycle of pelvic contractions could not be demonstrated, but pelvic pressure waves were caused by respiratory and muscular movements. In the hydronephrotic kidney the resting pressure corresponded with the degree of hydronephrosis as demonstrated by pyelography, and the pelvic pressure was increased during intravenous infusion of saline.

23. G. D. CHISHOLM, R. W. PIGOTT, and R. SHACKMAN, Postgraduate Medical School: "Intra-extracellular Osmotic Changes of Hæmodialysis".

Efficient hæmodialysis effects a 75 per cent reduction in the blood-urea levels of azotæmic acute oliguric patients. After hæmodialysis there is a rapid initial rise of blood-urea which is greater than would be expected. A constant daily rise of 50 mg. per 100 ml. before dialysis is increased to 85 mg. per 100 ml. during the day immediately after dialysis: thereafter, the rate returns to the previous values. Equilibration, determined by hourly observations, occurs in 15–21 hours. Evidence, based on muscle biopsy chemistry, suggested that the phenomenon reflected delayed diffusion of intracellular urea into the extracellular compartment. Direct determinations of plasma osmolarity during dialysis showed a direct relation between the changing urea concentrations and plasma osmolarity: a significant decrease of plasma osmolarity occurred when hæmodialysis effected efficient urea clearance from the blood and the extracellular compartment. Intra-extracellular osmotic gradients therefore appear to be an inevitable consequence of hæmodialysis and may be significant in the management of some patients with acute renal failure.

REVIEWS AND NOTICES OF BOOKS

Surgery of the Acute Abdomen. By JOHN A. SHEPHERD, V.R.D., M.D., Ch.M., F.R.C.S., Q.H.S., Consultant General Surgeon, Liverpool Region; Surgeon Captain R.N.R. 9 × 6 in. Pp. 1228 + xi. Illustrated. 1960. Edinburgh: E. & S. Livingstone Ltd. £5.

THIS is a large comprehensive work which covers every aspect of acute abdominal disease.

The author, with some 1179 abdominal emergencies to his credit, is well able to write on this subject which he has made his own.

There are some twenty-five chapters in the book, and at the end of each chapter there is a complete list of references.

The illustrations, especially the numerous plates, are excellent, and have been well chosen.

Sir Zachary Cope writes a foreword to this book, cordially recommending it to every general surgeon, and so do we.

Pages in the History of Chest Surgery. By RUDOLF NISSEN, M.D., and ROGER H. L. WILSON, M.B., B.Chir. 9 × 5¾ in. Pp. 166 + vii. Illustrated. 1960. Springfield, Ill.: Charles C. Thomas. (Oxford: Blackwell Scientific Publications Ltd.) 60s.

THIS is a useful book because it gives an account of the great pioneers who by their efforts have played an important part in the development of chest surgery in the last seventy-five years. The authors have done their work well on the whole, but it is a pity that the name of Sir William Macewen is not mentioned as the first surgeon to perform a pneumonectomy.

It is pleasing to see the pictures of these pioneers of chest surgery, and to read part of their original contributions as they were published in the various journals of the world literature.

The changing face of surgery can be seen in the way pathological anatomy has given place to the surgery of physiological dysfunction.

Students of Medical History will be delighted with this book, which traces the various interesting developments which have taken place in chest surgery over the last century.

Principles of Surgical Practice. By EMANUEL MARCUS, M.D., Ph.D., and LEO M. ZIMMERMAN, M.D. 10 × 7 in. Pp. 430 + x, with 58 illustrations. 1960. London: McGraw-Hill Publishing Co. Ltd. 97s.

THIS is a book which should prove of value to the senior medical student who wishes to obtain an overall picture of surgery. The average text-book of surgery does not devote enough space to the principles of surgical practice, and it is this gap that the authors have sought to fill.

Such problems as 'Surgical Microbiology and the Management of Infection' are dealt with in a masterly fashion. The total management of the surgical patient, including the pre-operative, operative, and post-operative periods, is another chapter which is outstanding.

This is an excellent revision book for any higher surgical examination.

Year Book of Cancer, 1959–60. Edited by RANDOLPH LEE CLARK, jun., and RUSSELL W. CUMLEY. 7¼ × 5 in. Pp. 533, with 172 illustrations. 1960. Chicago: Year Book Publishers Inc. (London: Interscience Publishers Ltd.) 64s.

THE 1959–1960 *Year Book of Cancer* covers a wide field and is well illustrated. As one would expect, the majority of articles referred to in this book are of American origin, but there are some from English and other sources.

The problem of leukæmia is covered in an excellent way. The recorded case of leukæmia in an infant born to a mother with leukæmia raises questions concerning transmission of a filterable leukæmogenic agent from mother to fœtus.

The question of cancer in children is well covered in this volume.

We consider that this is one of the more important volumes of the 1959–1960 series, and every surgeon should have a copy for reference purposes.

The Reluctant Surgeon. The Life of John Hunter. By JOHN KOBLER. 8½ × 5½ in. Pp. 359. 1960. London: William Heinemann Ltd. 21s.

ANOTHER book on John Hunter—is there anything new to write about? This is the question which the reviewer asked himself before reading this book. What is the answer? John Kobler has extensively studied the various works of John Hunter and the enormous bibliography dealing with Hunter, his works, his life, and his museum.

He has written an interesting book, which will prove really attractive to the layman and to the medical man, but there are some mistakes, such as Hunter's fellowship of the Royal Society of Medicine, which was of course impossible, because Hunter died many years before this Society was founded.

The author has written quite a lively book on John Hunter, and the price is most moderate.

Complications in Surgery and their Management. Edited by CURTIS P. ARTZ, M.D., F.A.C.S., and JAMES D. HARDY, M.D., F.A.C.S. 10 × 6¾ in. Pp. 1075 + xlvii, with 272 illustrations. 1960. Philadelphia and London: W. B. Saunders Co. Ltd. £8 1s.

THIS is a large and comprehensive work in which no less than sixty-nine contributors have written articles dealing with every facet of the problem of surgical complications. On reading through this exhaustive volume, one is struck with the mixed variety of rare complications which may from time to time follow surgical intervention.

The book is full of ultra-modern American terminology such as 'thrombectomy', but the descriptive matter reads well.

There are some illustrations, all of which have been carefully chosen and are well reproduced.

This is a work for the young surgeon, but not for the student, who would have difficulty in seeing the wood for the trees.

As a reference volume on surgical complications it could not be bettered. All medical libraries should have this book.

Diagnostic Roentgenology of the Digestive Tract without Contrast Media. By BERNARD S. WOLF, MANSHO T. KHILNANI, and ARTHUR LAUTKIN. 10 × 6½ in. Pp. 180, with 245 illustrations. 1960. New York: Grune & Stratton. $8.75.

ALTHOUGH intended primarily for radiologists, this monograph, produced by the Staff of the Department of Radiology in the Mount Sinai Hospital, New York, may be read with interest by all who are concerned in the diagnosis of disease of the alimentary tract.

Starting with a number of cases in which considerable diagnostic difficulty was encountered, and in which several radiological investigations had been made, the authors found that careful re-examination of the earlier films showed findings which, in retrospect, were diagnostic of the lesion. They have since re-examined a large number of such cases and now present their findings in this monograph.

The opening chapter is on general principles, in which the physical and physiological laws governing the presence of gas in the bowel are simply and clearly summarized. The authors then give examples of a variety of gastro-intestinal lesions which may be recognizable on plain films of the abdomen.

Despite the inevitable loss due to the process of reproduction, the numerous illustrations are almost all of an extremely high standard. Scrutiny of films of the abdomen in the light of the authors' experience may well, in the future, reduce the number of investigations undertaken on many patients before the diagnosis is determined.

Transactions of the International Society of Plastic Surgeons. Edited by A. B. WALLACE, M.Sc., F.R.C.S. (Ed.). 9¾ × 7 in. Pp. 589 + xxiv. Illustrated. 1960. Edinburgh: E. & S. Livingstone Ltd. 90s.

THIS is a stimulating volume to read, for it demonstrates in no uncertain manner the great strides that have been made in plastic surgery throughout the world.

The second international congress was held in London in 1959, at the Royal College of Surgeons of England, Mr. Rainsford Mowlem being the President. His Royal Highness the Duke of Edinburgh sent an address of welcome from Buckingham Palace. Sir James Paterson Ross welcomed the guests to the College.

These transactions are divided into sixteen sections dealing with every aspect of plastic surgery, from the treatment of cleft lip and palate to cosmetic operations.

Many surgeons from Europe, America, and the Far East took part in these lectures and discussions.

The volume is illustrated by many clinical photographs, radiographs, and photomicrographs, all of which are of a high order. Plastic surgery lends itself to photographic expression, for it is so important for record purposes to have photographic records before and after operation.

This is an excellent volume, and it does great credit to the Editor, who has so skilfully arranged the various sections.

Modern Trends in Cardiac Surgery. Edited by H. R. S. HARLEY, M.S., F.R.C.S., Consultant Thoracic Surgeon, United Cardiff Hospitals. 9½ × 6½ in. Pp. 282 + xiii, with 79 illustrations. 1960. London: Butterworth & Co. (Publishers), Ltd. 70s.

THIS is an all-British production of which the profession may well be proud. The twenty-two contributors have covered all aspects of Cardiac Surgery as practised in the British Isles to-day.

There can be little doubt that during the last decade the surgery of the heart has become commonplace, and the surgeons of the future will look to this book as their guide and reference volume. The time cannot be far distant when the cardiac surgeon will have to devote his attention to the problem of the inadequate coronary blood-supply.

Sir Clement Price-Thomas, who writes a foreword to this book, is rightly enthusiastic as to its value, and its publication comes at an opportune time.

A very worthy volume for the well-known 'Modern Trends' series.

Modern Trends in Urology. Second Series. Edited by SIR ERIC RICHES, M.C., M.S., F.R.C.S., Surgeon and Urologist, The Middlesex Hospital, London. 9½ × 6½ in. Pp. 300 + xvi, with 123 illustrations. 1960. London: Butterworth & Co. (Publishers), Ltd. 70s.

THIS is an excellent volume covering the whole field of urological surgery and dealing with the pathology of the various tumours of the urinary tract.

Sir Eric Riches has managed to gather around him an outstanding team of experts, all writing on their own special subjects.

When the first series on *Moderns Trends in Urology* was published some years ago under the editorship of Sir Eric Riches, the field covered was somewhat different. For this second series an up-to-date presentation of urological surgery and medicine is made. The volume demonstrates the part played by biochemistry and pathology in the treatment of urological conditions.

The outstanding contribution to this volume is undoubtedly that dealing with carcinoma of the bladder and the results obtained by supervoltage therapy by Riches and Windeyer. Earle's article on Granulomatous Prostatits is also of a high order.

The various papers which make up this volume strike a realistic balance between medicine and surgery, making it not only of value to urologists, but also to gynæcologists, general surgeons, and pathologists.

One of the best volumes in the now well-known 'Modern Trends' series.

I Tumori Retroperitoneali. By G. F. PELLEGRINI and G. CARAFFA. 9½ × 6¾ in. Pp. 306 + xii, with 179 illustrations. 1960. Milan: Edizioni Minerva Medica.

THIS monograph is based upon the direct observation of 54 patients with retroperitoneal tumours (defined as new growths arising in the posterior extraserous tissues of the abdominopelvic cavity, excluding those below the pelvic inlet and those arising primarily in the adrenal, kidney, pancreas, or mesentery). After dealing with the historical, anatomical, and embryological aspects of the subject, the clinical features are fully treated. The account of symptomatology includes reference to a number of recent reports of endocrine-active tumours, while the section on radiological investigation is lavishly illustrated with plates showing the value of plain radiography, barium studies, urography, cholecystography, and cholangiography, aortography, retroperitoneal insufflation, and combinations of these. Differential diagnosis, treatment, and prognosis are then considered, while the last hundred pages or so present the individual clinico-pathological features of each of the various types of tumour. A tabulated list of the authors' cases and a bibliography of about 500 references conclude the book. Altogether this is a useful record of experience in one of the less familiar branches of surgery and a valuable directory to an elusive topic.

The Physiology of the Mouth. By G. NEIL JENKINS, M.Sc. (L'pool), Ph.D. (Cantab.), Reader in Oral Physiology, Medical School, King's College, Newcastle upon Tyne. Second edition. 8¾ × 5½ in. Pp. 355 + xii, with 69 illustrations. 1960. Oxford: Blackwell Scientific Publications Ltd. 40s.

THE first edition of this book was hailed as an important contribution to our knowledge of oral physiology, a subject which had been greatly neglected over the years.

This second edition will enhance the reputation of the book, and it will become the reference volume on this subject.

The chapters on the physiological aspects of dental caries and on mastication and deglutition are superb. They are a notable contribution to our knowledge.

We are living in an age when biochemistry is to the fore, and this book will certainly take its place as an essential one in the student's library.

Illustrating Medicine and Surgery. By MARGARET C. MCLARTY, D.A. (Edin.). Artist, United Oxford Hospitals. 9¾ × 7 in. Pp. 159 + viii, with 178 illustrations. 1960. Edinburgh: E. & S. Livingstone Ltd. 37s. 6d.

THIS is a really useful book because it portrays the many ways in which the medical artist may help the writer of books or papers.

It is universally acknowledged that good illustrations greatly enhance the value of any text-book, or medical or surgical articles, whether they be in the specialist journals or in the weekly medical newspapers.

Miss McLarty is one of the early pioneers of medical artists, and she has covered an enormous field of medical illustration, including some of the War journals and books.

Although great strides have been made in the field of photography as applied to medicine in general, there is still a very definite place for the medical artist.

Every hospital of any size should have the services of a medical artist. This book will help to promote that suggestion.

Cancer, The Significance of Delay. By ROBERT SUTHERLAND, M.D., D.P.H., Director, British Empire Cancer Campaign (Yorkshire Council). 8½ × 5½ in. Pp. 206 + ix. 1960. London: Butterworth & Co. (Publishers), Ltd. 30s.

THIS is a useful book because it gives a very up-to-date survey of the deaths from cancer over the last fifty years. The author has reviewed the literature very thoroughly, and gives some interesting statistics. He quite definitely demonstrates how difficult it is to make an appraisal of the different forms of treatment.

There are so many variables to be considered as far as prognosis is concerned, the most important being: (1) Tumour characteristics; (2) Host characteristics; (3) Environment.

The author gives some engaging figures regarding the duration of the disease and the ultimate prognosis. He says: "In round figures, only one out of every three patients with breast cancer, operable or inoperable, will be alive five years after the cancer is discovered". This is a depressing thought.

There are a few mistakes in this book; for instance, Sir Lenthal Cheatle is referred to as Sir Lentham Cheatle.

This book should prove of value as a reference volume.

The Metabolism of Oral Tissues. Annals of the New York Academy of Sciences, Volume 85. Edited by PHILIP PERSON. 9 × 6 in. Pp. 499, illustrated. 1960. New York: Academy of Sciences. $4.50.

THIS series of thirty-three papers was read at a conference held in New York in October, 1959, and they have now been bound together in paper-back form at a very reasonable price.

To quote from R. F. Sognnaes's introduction, the conference was an attempt to review the current knowledge of the mouth over and beyond the dental apparatus and to cover the entire problem of the development, structure, environment, and metabolism of tissues in the oral cavity. In doing this, enamel, dentine, alveolar bone and gingival tissues, and salivary gland are closely examined by the most recent methods including electron microscopy, cytochemistry, enzymology, and crystallography to investigate the basic mechanisms of calcification, cornification, and secretion, as well as of host-parasite relationship.

In a collection of papers by so many authors there are bound to be differences in the standard of presentation, but the overall standard is pleasingly high and the illustrations are of very high quality and well reproduced.

This book should provide a mine of information regarding recent trends in research into tissue behaviour in this region and is thoroughly recommended to those who are interested in any aspect of this work.

Fourth Tissue Homotransplantation Conference. Annals of the New York Academy of Sciences, Volume 87. Edited by JOHN MARQUIS CONVERSE. 9 × 6 in. Pp. 607, illustrated. 1960. New York: Academy of Sciences. $5.00.

THE report is divided into five sections and includes the extempore discussions. Section One, containing work on immunogenetics and phylogenetics, reflects the growing quantity of research on inbred animals other than mice. The second section covers variations in response to tissue transplants. Zotikov describes prolonged acceptance of histo-incompatible skin-grafts amongst rats when the graft exceeds one-third of the body surface. Evidence suggests that part of this prolongation is due to exposure of the recipient to a massive dose of antigenic material. Observations on patients with Hodgkin's disease are reported by the Minnesota group; they found absent or decreased capacity to develop delayed hypersensitivity, and abnormal skin-graft rejection rates. Section Three begins with a fine paper by H. S. Lawrence and his colleagues describing the transfer of homograft sensitivity by extracts of leucocytes. Other articles describe antibody effects and their possible relation to homograft problems. In the final two sections immunological tolerance, graft versus host reactions, and organ transplantation are considered.

Research workers interested in homotransplantation will wish to study most of the proceedings, and there is much to interest the less specialized reader.

Modern Concepts of Thyroid Physiology. Annals of the New York Academy of Sciences, Volume 86. Edited by RULON W. RAWSON. 9 × 6 in. Pp. 365, illustrated. 1960. New York: Academy of Sciences. $3.50.

THIS volume contains sections on intrathyroidal biochemical reaction, transport and metabolism of thyroid hormones, cellular mechanisms in actions of thyroid hormones and their analogues, and the chemistry and physiology of thyroid-stimulating hormone.

The standard of papers, as one would expect from those contributing, is very high, and Dr. Rulon Rawson, as Consulting Editor and Conference Chairman, deserves special mention. This volume is a 'must' for the doctor or scientist who is interested in the thyroid gland.

Connective Tissue and Diseases of Connective Tissue. Volume 86 of Annals of the New York Academy of Sciences. Edited by FRANKLIN N. FURNESS. 9 × 6 in. Pp. 258. Illustrated. 1960. New York: Academy of Sciences. No price given.

EVER since Klemperer focused attention, almost inadvertently, on the connective tissues of the body and on the possibility of their being the 'system' primarily implicated in certain diseases, workers in many diverse fields have used a wide variety of techniques to study the structure and function of this 'system'. This volume reports the latest of the several symposia held in the U.S.A. during the last decade, and it is striking how the contributors cover an even wider field than their predecessors. It ranges from Curran's paper on response *in vitro* of fibroblasts to dusts, to McKusick's review of 'Heredity and Connective Tissue Diseases'. The papers are of a high standard and Dr. Bernard Wagner, Chairman and Editor of the Conference, is to be congratulated on the quality of the publication.

It is highly recommended to those interested in connective tissue.

Numerical Properties of Functions of more than one Independent Variable. Edited by HENRY C. THACKER, jun. Volume 86 of Annals of the New York Academy of Sciences. 9 × 6 in. Pp. 197. 1960. New York: Academy of Sciences. $3.00.

IN many experimental situations the variable in which one is interested is affected in a complex way by many others. For example, the yield of a chemical compound may be influenced by temperature, pressure, *p*H, oxidation reduction potential, concentration of other compounds, and many other factors. This symposium is concerned with the mathematical methods available for the study of such complex situations.

Until recently, only small numbers of factors could be taken into account and their relationship to one another had to be of some very simple form. However, the arrival

of electronic computers provides opportunities for the study of much more complicated and realistic networks of causation. I do not know of any biological applications so far, but the general approach is of potential interest. A classical example of this kind of interrelationship in biology is the regulation of the *p*H of the blood as worked out by L. J. Henderson.

The articles under review are all austerely mathematical, and, as they stand, only likely to be of interest to specialists. However, in years to come it is likely that they will find applications in biology and medicine.

Disc Lesions and Other Intervertebral Derangements. By E. J. CRISP, M.D. (Cantab.), D.Phys.Med. (Lond.). 8½ × 5½ in. Pp. 158 + viii, with 48 illustrations. 1960. Edinburgh and London: E. & S. Livingstone Ltd. 15s.

THE commonest ills of the human spine are those least understood; vague pains and stiffness which, in the nature of things, cannot be investigated by exploration and on which radiography throws at best an uncertain light. Indeed the only two conditions with any sort of nosological respectability are the prolapsed intervertebral disk and degenerative (osteo-) arthritis of the spine, though in the latter there is often a depressing lack of correspondence between the radiographic appearances, which may be most abnormal, and the physical signs, which may be minimal. Dr. Crisp, having spent some years in general practice, is well aware of this, and the diagnosis and treatment of these minor disorders of the spine are the theme of this book. It is not a scientific treatise. He gives a good description of relevant anatomical features of the spine, but when he comes to explain some of the minor disorders we are told, for example, that acute back pain may be caused by the nipping of synovial fringes in the small intervertebral joints. This may be a reasonable hypothesis but it has never been proved and it might have been wiser to have confessed ignorance. As might be expected, he regards manipulation as the most generally useful method of treatment and the techniques he describes, if faithfully carried out, will undoubtedly give good results. But there are no figures to give any indication of the effectiveness of manipulation; this is a pity, because statistical surveys are necessary if the indications for and the limitations of any kind of treatment are to be clearly defined. This book will be of use chiefly to general practitioners and orthopædic surgeons. It is safe, and, within limits, sound.

Simplified Anatomic Instruments. By Professor PEDRO D. CURUTCHET, Buenos Aires. Pp. 123. 1960. Buenos Aires.

IN this book the author tries to demonstrate the fact that most common surgical instruments are badly designed. The common design of artery forceps has rings for the thumb and finger. Professor Curutchet considers that modified tubes would be more practical and more anatomically correct. Needle holders, dissecting forceps, and curettes are all designed with finger supports. Those illustrated in this small monograph are far more illuminating to the reader than the actual text.

It is doubtful if British surgeons will want to make use of these ultra-modern surgical instruments.

Atlas of Exfoliative Cytology. By GEORGE N. PAPANICOLAOU. Supplement. 11 × 8 in. 1960. Cambridge, Mass.: Harvard University Press. (London: Oxford University Press.) 44s.

THE second supplement of this well-known atlas contains some excellent coloured plates depicting the cytology of the female genital system, the urinary and male genital system, the respiratory system, the digestive system, and body fluids.

There is an excellent memorandum on staining, and this includes the detailed preparation of stains.

As a reference volume on exfoliative cytology this atlas could not be surpassed. The reproduction of the malignant cells is excellent.

Cancer Progress 1960. Edited by RONALD W. RAVEN, O.B.E. (Mil.), T.D., F.R.C.S. 9½ × 6½ in. Pp. 242 + xvi. Illustrated. 1960. London: Butterworth & Co. (Publishers), Ltd. 60s.

THIS is a useful reference volume, because it gives an up-to-date account of cancer research and progress, written by a large panel of experts drawn from all over the world, including Moscow.

Every facet of the cancer problem is covered in this volume, from tumour virology to the chemotherapy of solid tumours.

An excellent and comprehensive set of references is found at the end of each chapter.

We hope Mr. Raven will be able to produce such a book every year, for there can be no doubt that it fulfils a very definite need.

Congenital Deformities. By GAVIN C. GORDON, M.B., F.R.C.S.E. 9¾ × 6¼ in. Pp. 128 + viii, with 113 illustrations. 1961. Edinburgh and London: E. & S. Livingstone Ltd. 37s. 6d.

THIS is an attractive monograph on an important subject, and the author is to be congratulated on the manner in which he has marshalled his facts.

Congenital deformities of bones and joints are not uncommon in general practice, and such a book as this with its excellent radiographs should prove of real value to the busy practitioner.

The author, with his matured clinical background, has produced a most readable book, full of interesting facts. It is pleasing to see the radiographs of a congenital deformity before and after treatment.

The final result of treatment is perhaps the most important issue which should interest all clinical observers. This volume gives many examples of the result of treatment of many congenital deformities.

Resuscitation of the Newborn Infant. Edited by HAROLD ABRAMSON, M.D. 9¾ × 6½ in. Pp. 274. Illustrated. 1960. St. Louis: C. V. Mosby Co. (London: Henry Kimpton.) 75s.

THIS book is a scientific presentation of the various conditions which prevent the newborn babe from living. The book is written by a large body of clinicians, physiologists, anæsthetists, and obstetricians. The whole subject of resuscitation of the newborn infant is well covered.

The problems of anorexia, respiratory insufficiency, obstetric analgesia and anæsthesia, are but a few that are discussed to the full in this volume.

It is quite stimulating to find that the basic medical sciences have their part to play in the problem of resuscitation of the newborn infant.

The Hand: A Manual and Atlas for the General Surgeon. By HENRY C. MARBLE, M.D., F.A.C.S. 9½ × 6½ in. Pp. 207 + viii, with 58 plates. 1960. Philadelphia and London: W. B. Saunders Co. Ltd. 49s.

THE anatomy and the surgery of the hand are receiving much attention, and quite rightly so, for infection of the tendons and tendon-sheaths may play havoc with the usefulness of this part of the upper extremity.

It is quite refreshing to see some new and original drawings of the anatomy of the hand. The drawings of the cross-sections of the forearm and hand are quite outstanding, and should help both the student and the surgeon to refresh their memories of the various anatomical relationships.

The closed injuries of the hand are well described.

The treatment of burns is very practical and up to date, but why complicate the already difficult classification of burns by describing three degrees? Surely the most sensible and practical classification is simply to have two types, the superficial and the deep.

The section on amputations is good, and the drawings excellent.

A good book for the surgical registrar who has to deal with casualties.

Fundamentals of Nerve Blocking. By VINCENT J. COLLINS, M.S., M.D., with the assistance of E. A. RAVENSTINE, M.D. 9¼ × 5¾ in. Pp. 354, with 144 illustrations. 1960. London: Henry Kimpton. 71s. 6d.

THIS is a comprehensive volume covering every aspect of nerve-blocking, both for regional anæsthesia and for therapeutic purposes.

With the increase in drugs which produce anæsthesia with practically no toxic effects, regional anæsthesia may be said to have come into its own.

For idiopathic neuralgias, nerve-blocking produces instant relief of pain, while such conditions as periarthritis (frozen shoulder) and post-coronary pain often derive much benefit from this form of treatment.

This book should prove of value not only to the anæsthetist but also to the surgeon and the neurologist.

This is an excellent reference volume on nerve-blocking.

Cancer in Childhood and Youth. By SIGISMUND PELLER, M.D., F.R.S.H. 8¾ × 5¾ in. Pp. 291 + xii, with 29 illustrations. 1960. Bristol: John Wright & Sons Ltd. 42s.

THIS is a companion volume to *Cancer in Man*, which was published in 1952. The author holds very definite views as to the causation of cancer, and though they are not universally accepted, they are interesting and constructive. We know very little about the aetiology of cancer, except that it is a many-sided problem.

Recently, much interest has been taken in childhood cancer, and this has been stimulated by the increase in leukæmia.

This book provides entertaining reading, and the author has divided up the subject of cancer in childhood into twenty-two chapters. The most interesting chapter is that devoted to cancerogenesis and transplacental infection.

Everyone interested in cancer should read this book, because it is provocative and interesting.

The price of the book is most moderate.

Surgery for Nurses. By JAMES MARONEY, M.B., Ch.B., F.R.C.S. (Eng.), L.R.C.P. (Lond.). Seventh edition. 8½ × 5½ in. Pp. 792 + xii, with 621 illustrations. 1960. Edinburgh: E. & S. Livingstone Ltd. 32s. 6d.

THE new edition of this text-book is improved by the addition of sections on 'Acute Circulatory Failure' and 'Fluid and Electrolyte Balance', and some of the accompanying diagrams are very helpful; but there is still room for further improvements. In view of the recent work of hospital cross-infection committees the chapter on 'Asepsis and Theatre Technique' would benefit by revision, and the description of nursing care of the patient in the chapter headed 'Injury and Disease of the Central Nervous System' needs amplifying. Minor criticisms are the omission of reference in the chapter entitled 'Oxygen Therapy' to the importance of rate of flow, moistening of the oxygen, and the care of the patient's skin and mucous membrane when a nasal catheter is used.

The picture of a patient being nursed in an oxygen tent with her head completely unsupported is unfortunate. In the chapter on 'Disease of the Thyroid Gland' the author suggests tepid sponging when the patient is sweating. It is surely wrong for this treatment to be applied when the temperature is falling.

Nouvelle Pratique Chirurgicale Illustrée. By JEAN QUÉNU. Part XVI. 10½ × 7 in. Pp. 296, with 248 illustrations. 1960. Paris: G. Doin. 41 NF.

TO study a particular operation before setting out to do it oneself, it is best to watch an expert at work. Second only to this, a series of clearly drawn, well-described illustrations, preceded by brief notes on indications, management, and results, forms a valuable means of learning operative technique. This series of volumes, of which the present contribution is the sixteenth, provides such information with praiseworthy clarity. A wide range of procedures are covered, including extended right pneumonectomy for lung carcinoma, pelvic floor repair, plastic reconstructions for hydronephrosis and for ureteric stricture, and plating of a tibial fracture. An ingenious ileal graft is depicted for left colectomy where obesity combined with a short mesocolon renders colo-colic anastomosis difficult.

One notes with considerable misgivings that Whitehead's operation for hæmorrhoids is described; the risks of late stricture formation must be immense.

Although this book provides an interesting cross-section of French surgical techniques, the general plan of this series makes ready reference difficult; thus one has to refer to several volumes for an overall picture of, say, operations on the stomach or colon. There seems nothing to commend this heterogeneous arrangement which one would like to see altered in subsequent editions.

BOOK NOTICES

[The Editorial Committee acknowledge with thanks the receipt of the following volumes. A selection will be made from these for review, precedence being given to new books and to those having the greatest interest to our readers.]

Surgical Treatment of Unequal Extremities. By CHARLES WEER GOFF, M.D. 11 × 8½ in. Pp. 184 + x, with 136 illustrations. 1960. Springfield, Ill.: Charles C. Thomas. (Oxford: Blackwell Scientific Publications Ltd.) 88s.

Report of Committee III on Protection Against X-rays up to Energies of 3 MeV and Beta- and Gamma-rays from Sealed Sources. 9¾ × 7 in. Pp. 84. Oxford: Pergamon Press Ltd.

Le cisti e i tumori primitivi del mesentere. By FRANCESCO FONTANA. 9½ × 6½ in. Pp. 130. Illustrated. 1959. Bologna: Cappelli Editore.

La Radiculographie Lombaire dans la Sciatique. By J. ECOIFFIER. 9½ × 6½ in. Pp. 140, with 37 figures and 51 plates. 1960. Paris: Masson et Cie. 40 NF.

Klinische Chirurgie für die Praxis. Edited by O. DIEBOLD, H. JUNGHANNS, and L. ZUKSCHWERDT. Volume III, Part 2. 10¾ × 7 in. Pp. 212, with 63 illustrations. 1960. Stuttgart: Georg Thieme. DM.40.

Abstracts of Japanese Medicine. Vol. I, No. 1, October 1960. 9¾ × 6½ in. Pp. 188. 1960. Amsterdam: Excerpta Medica Foundation. Annual subscription. U.S. $30.00.

The Management of Fractures and Soft Tissue Injuries. By the Committee on Trauma, American College of Surgeons. 8½ × 5 in. Pp. 372 + xix. 1960. Philadelphia and London: W. B. Saunders Co. Ltd. 35s.

Urology in General Practice. By IAN PARTON, M.B., Ch.B., B.Sc. (N.Z.), F.R.C.S. (Eng.), Assistant Urologist, Auckland Hospital, New Zealand. 8½ × 5 in. Pp. 293 + xii, with 35 illustrations. 1960. London: Butterworth & Co. (Publishers) Ltd. 45s.

Modern Trends in Cardiology. Edited by A. MORGAN JONES, M.Sc.,M.B., F.R.C.P. 9½ × 6½ in. Pp. 264 + x. Illustrated. 1960. London: Butterworth & Co. (Publishers) Ltd. 70s.

Tools of Biological Research. Edited by HEDLEY J. B. ATKINS, D.M., M.Ch. Oxon., F.R.C.S. Eng., Hon. F.A.C.S., Director of the Department of Surgery, Guy's Hospital. Second series. 8¾ × 5½ in. Pp. 175 + xii, illustrated. 1960. Oxford: Blackwell Scientific Publications Ltd. 37s. 6d.

Pathology of Tumours. By R. A. WILLIS, D.Sc., M.D., F.R.C.P., Consultant Pathologist to the Imperial Cancer Research Fund, London. Third edition. 9½ × 6½ in. Pp. 1002 + xvi, with 500 illustrations. 1960. London: Butterworth & Co. (Publishers) Ltd. 105s.

First Aid in the Factory. By LORD TAYLOR, B.Sc., M.D., F.R.C.P., Medical Director, Harlow Industrial Health Centre. 8¾ × 6 in. Pp. 140, with 71 illustrations. 1960. London: Longmans, Green & Co. Ltd. 9s. 6d.

Klinische Chirurgie für die Praxis. Edited by O. DIEBOLD, H. JUNGHANNS, and L. ZUKSCHWERDT. Volume I, Part 4. 10¾ × 7¼ in. Pp. 936, with 201 illustrations. 1960. Stuttgart: Georg Thieme. DM.54.

Lectures on the Scientific Basis of Medicine (British Postgraduate Federation). With various contributors. Vol. 8. 1958–59. 8½ × 5½ in. Pp. 467. Illustrated. 1960. London: Athlone Press. 45s.

The Nuffield Foundation Fifteenth Report. 8½ × 5½ in. Pp. 144. 1960. London: The Nuffield Foundation.

Biochemical Aspects of Microbial Pathogenicity. Annals of the New York Academy of Sciences, Volume 88. Edited by WERNER BRAUN. 9 × 6 in. Pp. 1021–1318. Illustrated. 1960. New York: Academy of Sciences. $5.00.

Biochemistry and Pharmacology of Compounds derived from Marine Organisms. Annals of the New York Academy of Sciences, Volume 90. Edited by ROSS F. NIGRELLI. 9 × 6 in. Pp. 615–950. Illustrated. 1960. New York: Academy of Sciences, $5.00.

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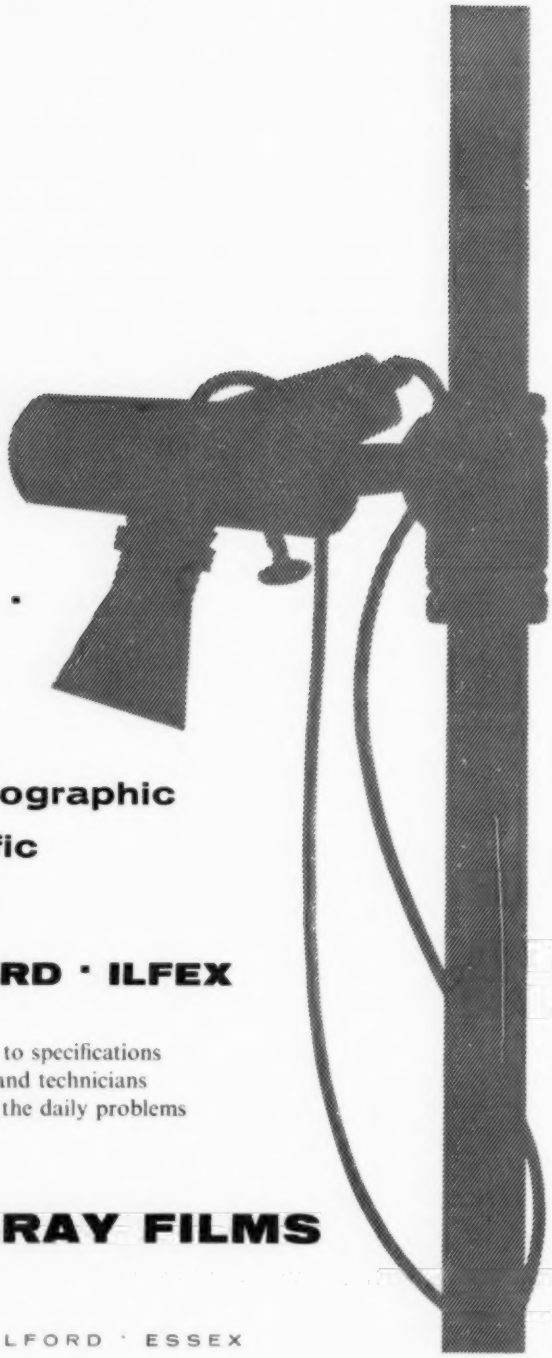

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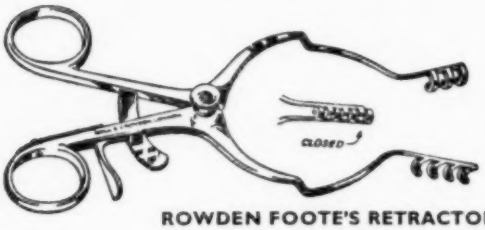

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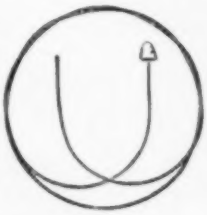

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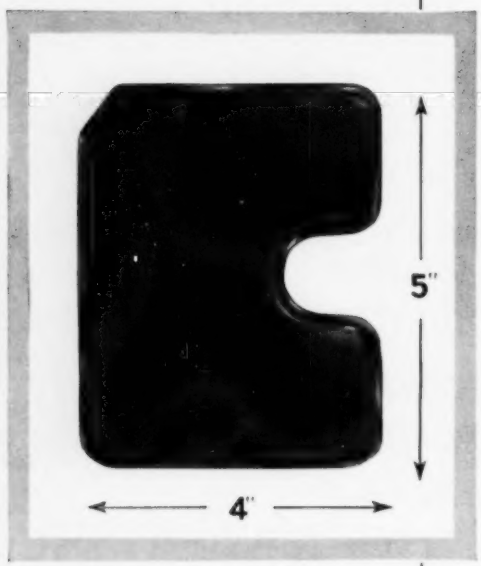
The renogram and kidney surgery



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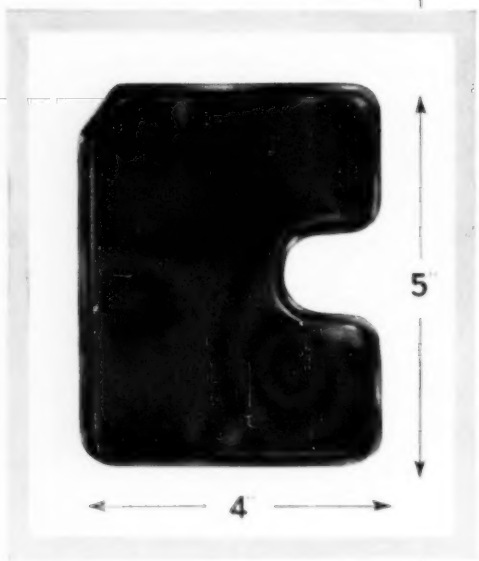

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